



The uncertain effect of menopause on blood pressure

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Abstract

In affluent societies blood pressure increases with age from early life to the eighth decade with sex differences. Before middle age, lower blood pressure values are observed in women than in coeval men, whereas the reverse seems to occur thereafter. Menopause is considered the major determinant of blood pressure rise in women. If this hypothesis is well-founded, menopause can be regarded as one of the main cardiovascular risk factors, involving more than half of the human population, as well as the most ineluctable. In industrialized countries, age at menopause ranges between 50 and 52 years. The popular message is that fertile women are protected from cardiovascular risk by circulating estrogens, a privilege that is lost when postmenopausal women become not different from men from the point of view of risk factors and cardiovascular events. Nevertheless, the hypothesis that menopause or the estrogen decrease are per se associated to blood pressure increase is still under debate. Indeed, the epidemiological challenge is due to the coincidence between advancing menopause and aging, and also to the evidence that both menopause and blood pressure have common determinants such as body mass index, diet, smoking, and socio-economic class. The strongest doubt is whether menopause is a dependent or independent risk factor for high BP, i.e. whether its action on blood pressure—if any—is due directly to estrogen fall or to other indirect factors.

The controversial behavior of blood pressure in menopause

Menopause in the eyes of the epidemiologist

Natural menopause is reached when the follicular reserve is depleted to approximately 1,000, in turn resulting in reduced ovarian production of estradiol (E_2) to approximately 10% of premenopausal levels [1]. Indeed, at menopause E_2 levels fall precipitously, while levels of estrone decline to a lesser extent [1].

Unfortunately, the epidemiological terminology used to classify natural menopause relies on self-reported menstrual patterns because information on hormonal status is rarely available at a population level. Therefore,

premenopausal women (also defined as fertile) are labeled as the ones who have experienced no menstrual changes, and natural postmenopausal women as those who have had one year of consecutive amenorrhea in the absence of oophorectomy or other treatment. *Climacteric*, the period of life starting from the decline in ovarian activity until after the end of ovarian function, is defined as the 2–8 years preceding menopause and 1 year following final menses. This classification is the first cause of controversy, as menstrual patterns may provide misleading information about ovarian function.

At a superficial reading, the medical literature seems to agree in defining natural menopause as a hypertensive factor. The protective effect of estrogens in premenopausal women has been taken for granted so much that the articles on this topic have ended up to quote themselves in a self-referential spiral. However, a presumptive independent direct association between menopause and blood pressure (BP) is extremely uncertain, and different cross-sectional surveys reported elevated [2, 3], unchanged [4], or even reduced [5] BP after the climacteric. Additionally, most longitudinal studies suggest that menopause per se is not associated with hypertension or with a BP increase [4], while few others report a positive independent association between menopause and high BP [6, 7].

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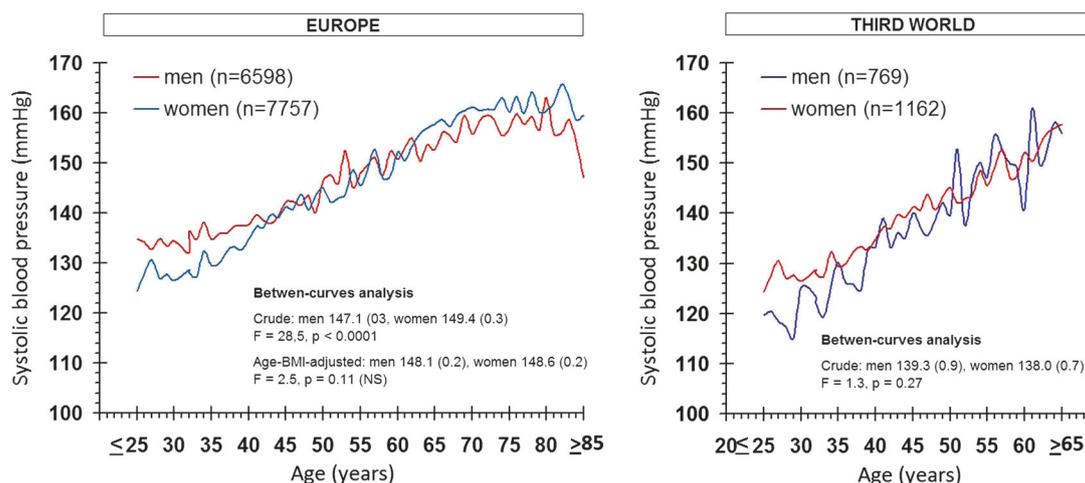


Fig. 1 Systolic blood pressure in relation to age adjusted for body mass index in men and women in general population from Europe [4, 8, 12] (left panel, $n = 6,598$ ♂, $n = 7,757$ ♀) and from developing countries [9–11] (right panel, $n = 769$ ♂, $n = 1,162$ ♀; also due to courtesy of

Both cross-sectional and longitudinal analyses have some limitations. Inability to assess temporal relationships and no possibility to establish a true cause → effect relationship are the limitations of the former, while the latter may lead to over- or under-estimation of the relationships over time due to changes in the environmental conditions, first of all medications. Inclusion of women oophorectomized or on hormonal replacement therapy (HRT) are other confounding factors.

Figure 1 (left panel), based on cross-sectional analysis derived from general population data ($n = 14,355$) previously described [8] and integrated with new cases, illustrates the question on *BP vs. age curves* in men and women. The two curves cannot be statistically separated from each other when age and body mass index (BMI) are included in the analysis as confounders. If we accept to stratify our data *a priori* (an operation that it is not statistically appropriate), BP seems to be visually higher in men than in women in the very early ages (<42 years, $p < 0.0001$), then the two curves overlap except for the periods between 50 and 55 years (when BP is significantly higher in men, $p = 0.002$) and after 62 years (when BP is significantly higher in women, $p < 0.0001$). It is evident that the apparent crossovers in the curves represent nothing in particular and such age-related changes are arbitrary, not related to menopause. Furthermore, contrary to what it would expect, at the age of 40–55—corresponding to the climacteric—BP is even higher in men.

BP vs. age curves are also different in different populations. In the right panel of Fig. 1, concerning 2961 untreated and unselected primitive men and women from developing countries [9–11], men have higher BP only until the age of 29 years, then the curves overlap with women never

prof. Paolo Pauletto). No difference is detectable between sexes, and the sex-specific curves show multiple crossovers without any point corresponding to presumptive menopause. At the age including the climacteric (about 40–55 years), blood pressure is even higher in men

showing BP values higher than those of men, independently of menopause.

It is therefore evident that the multiple crossovers in Fig. 1 represent nothing more than population dynamics deriving from a sum of factors, for instance the renin–angiotensin–aldosterone system (RAAS), the difference in muscle mass increase, and the impact of anti-hypertensive treatment which differs across sex due to lower compliance in women and to the presence of surviving men with lower BP. Actually, it is impossible to infer the age of menopause from *BP vs. age curves*.

Age and BMI, two uncomfortable confounders

As both menopause and BP changes are strictly linked to growing old, the effects of menopause and age are indistinguishable in practical terms. Therefore, in all the analyses aimed at clarifying if BP increases in menopause, age is the main and most uncomfortable confounder.

As age-adjustment is often insufficient, one possible statistical solution to abolish at all the confounding effect of age is to age-match women by menopausal status with the case-to-case matching procedure. For instance, a fertile woman aged 39 years is matched with a postmenopausal women aged 39 years and so on for each couple of women, until possible. This generates two cohorts having the same number of women and exactly the same age and standard deviations. The result of this procedure is shown in Fig. 2, derived from our general population previously described [4, 8, 12] and then extended to other cases, which includes two coeval cohorts of 697 women each, one of fertile and one of postmenopausal women. It is noteworthy that, once eliminated the confounder *age*, BP does not differ between

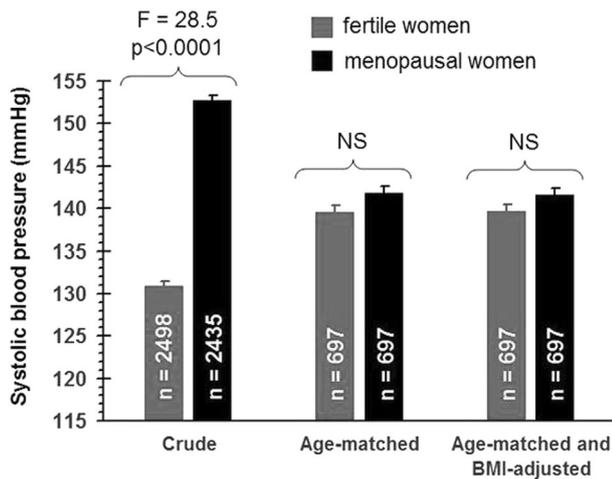


Fig. 2 Systolic blood pressure in fertile and postmenopausal women in general population from Europe [4, 8, 12]. Blood pressure is apparently higher in the latter, a difference that disappears when women are age-matched and even more when further are adjusted for body mass index (BMI)

the two cohorts. In some cases, this method can leave residual differences due to other confounders associated with menopause [5], for instance, an increase in adiposity that is progressive and age-related [13]: once adjusted for BMI or skinfold thickness, any differences definitely disappear.

Few research groups have longitudinal population-based data suitable to address the problem of menopause. Here too there is the problem of the confounding effects of age and BMI. During the follow-up of a cohort of women expecting menopause, as time goes by, there is an obvious increase in age and a demonstrated increase in BMI due to metabolic changes linked both to aging and to the menopause itself.

Now, the impact of obesity on BP is disproportionate in women compared with men, and BP is more heavily associated with increasing BMI in young obese women [14]. In a general North-European population involving 15,145 subjects, Wilsgaard et al. [14] demonstrated that BMI increase had a greater effect in increasing BP in women than in men, a phenomenon which was not associated with menopause. Therefore, statistical analysis must always take into account variations of age and BMI. Based on a longitudinal study [4], we divided women into three groups according to natural menopausal status: those that remained fertile, those that were already in menopause at the initial screening, and those that became menopausal. After adjustment for *age variation over time*, there was no difference in BP values in the three groups. In other words, the transition *from premenopausal to postmenopausal status* did not produce any BP increase. Goodman et al. [15] confirmed our results among 187

fertile and 159 postmenopausal women living in Honolulu: after adjustment for age effects, no clinical conditions, other than those attributable to the effects of aging, were significantly associated with menopause. Khitan et al. [16] also showed that in regression models only BMI was a significant predictor of systolic BP, independent of menopausal status.

Sporadic reports did not confirm this evidence [2, 3]. In one study including 462 North-European women, both systolic and diastolic BP were related to menopause independent of age and BMI (the odds of having hypertension in premenopausal was 2.2, $p = 0.03$) [3]. In addition, the association between BP and age was steeper in menopause. In another study involving 18,326 South-European women aged 46–59 years, after adjustment for age, BMI, smoking, and HRT, systolic and diastolic BP were higher in postmenopausal than in premenopausal women only in the two youngest age strata [2]. In a 5-year prospective analysis on 315 women aged 30–70 years randomly selected from general population and matched for age and for rank of BMI with 315 men [6], Staessen et al. found that systolic BP increased of about 5 mmHg/decade more in postmenopausal than in premenopausal women, and of approximately 4 mmHg during the follow-up in the latter, indicating that menopause per se could have potentiated the age-related increase in systolic BP (an increase that was putatively attributed to a reduction in arterial compliance) [7]. Postmenopausal women also had a steeper slope of 24-h pulse pressure on age than premenopausal, and higher carotid-femoral pulse-wave velocity, even after adjustment for age, 24-h BP, and BMI. However, in our general population of 1,853 men and women, an age-adjusted analysis found comparable arterial stiffness in fertile and postmenopausal women as expressed both as augmentation index and femoral-carotid pulse-wave velocity [17], and reactivity to stressor stimuli was not different as well [12]. These different findings on arterial compliance could be explained by differences in the echo-genetic context [18].

Three quasi-experimental models

The climacteric

The climacteric, an interesting separate phase in the transition from the reproductive to the non-reproductive state, represents *de facto* a sort of experimental model in which ovarian hormone concentrations waxy during months or years.

The climacteric seems to be critical for the development of early subclinical vascular damages. It seems the estrogen deficit from peri- to postmenopausal stage causes endothelial dysfunction and predisposes to inflammation,

vasoconstriction, and increase vascular permeability leading to atherosclerosis.

Some authors suggested that systolic BP increases in this phase by approximately 3–4 mmHg over 5 years in postmenopausal women [6]. In this case too, one possible explanation is that women who have gained weight during menopause are more exposed to BP increase. Others found, on the contrary, no change in systolic or diastolic BP around menopause. Moreover, when in our above-mentioned women (Fig. 1, left panel) the analysis was limited to the age of the climacteric ± 1 standard deviation, higher BP values were even recorded in men than in women: this contradicts the belief that the climacteric represents a cross-inversion in the BP vs. age curves across sexes.

Surgical menopause

Surgical menopause (cessation of menstruation following removal of both ovaries with or without hysterectomy) is also a sort of experimental model. Natural menopause is a progressive phenomenon, and age too increases progressively, making the analysis complex and uncertain as there is time for the organism to reset to the new status. This does not happen in surgical menopause, where a woman is admitted to hospital as premenopausal in the morning and is postmenopausal in the afternoon. If the presumptive pressor effects of menopause would be due to estrogen decrease, we would expect that such a woman shows higher BP values in the short period after oophorectomy. On the contrary, in general populations, comparable values of BP with conservation of the pre-existing circadian rhythm of ambulatory BP was found before and 6 months after bilateral oophorectomy [8]. Comparable results were found after 16 years [19]. This trend is true not only for hypertension but also for dyslipidemia and diabetes [20].

To complicate the picture, mere hysterectomy without oophorectomy can be followed by BP variations. Laughlin-Tommaso et al. [21] demonstrated in a longitudinal study that women undergoing isolated hysterectomy with ovarian conservation had apparently higher frequency of cardiovascular risk factors, but, after adjustment for other risk factors, obesity was the unique determinant of the association. It is therefore possible that cessation of menses, rather than the estrogen fall, is the cause of some of the adverse effects attributed to menopause [22]: apart from an increase in blood viscosity [23], lack of menses leads to loss of the menstrual periodic iron dispersion, considered by someone as protective for the cardiovascular system in women [24, 25].

Lessons from clinical trials

A clinical trial is a good approximation to experimental setting. The three major placebo-controlled clinical trials

calling into question the assumed protective effect of estrogen, the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) I and II, showed that HRT with conjugated equine estrogen (CEE) and progestin—or CEE alone—failed to provide cardiovascular prevention [26, 27].

The effect of HRT on BP is controversial because it has never been the primary endpoint in those trials. In observational studies, HRT is associated with lower BP values, while in randomized clinical trials conflicting results are observed. Differences in cohorts and methods of measuring BP partially explain these discrepancies. Indeed, recent vs. late postmenopausal may differ in their response to HRT. In a new evaluation of WHI, younger postmenopausal women taking estrogen showed a significant reduction in coronary heart disease after years 7–8, probably involving BP, although it was not an endpoint evaluated in this study. On the contrary, smaller studies on transdermal E_2 performed in recently postmenopausal women showed a 24-h BP reduction.

The HRT effect may also vary depending on the type of estrogen used (CEE or E_2), dosage, route of administration (oral or transdermal), and the progestin molecule eventually associated. For HRT to mimic premenopausal physiology, it is necessary to administer E_2 . However, CEE—that has been used in the WHI and HERS I and II trials—is rich in E_1 [1] and contains androgens that could counterbalance the estrogen pressor effects. In short-term studies, transdermal E_2 , given for 12 and 24 months, reduced diastolic and mean BP in normotensive postmenopausal women, while, if used for at least 5 years, it had no effect on BP or even increased it. Both estrogen and progestin may directly influence vasodilation, but their effect may be additive or antagonistic. Therefore, most scientific societies are now recommending to limit HRT to treatment of perimenopausal symptoms only, keeping dose and duration as low as possible and evaluating periodically health conditions.

If BP increases in menopause, why?

Although epidemiology is the first necessary approach to answer the question whether or not BP increases with menopause, the next step is to wonder whether sex steroids play a role in this, and—if so—whether this role is achieved indirectly (through intermediate phenotypes) or directly. Here, we briefly review the plausible mechanisms by which hormonal changes may lead to high BP in perimenopausal and postmenopausal women. We will also have a brief look to other mechanisms involved, such as sympathetic activation and obesity.

The estrogen hypothesis

In the last decades, many studies have tried to elucidate the pathophysiological mechanisms by which, in menopause, the observed E_2 levels fall could increase BP. Some authors observed that, during the luteal phase of the menstrual cycle, when E_2 levels peak, BP decreases. It has been also shown that estrogens modulate the vascular function by targeting estrogen receptors, namely estrogen receptor alpha ($ER\alpha$) and beta ($ER\beta$), in endothelial cells and in vascular smooth muscle cells, via genomic and non-genomic signaling [28]. $ER\alpha$ signaling, following estrogen binding, implies dimerization and nuclear translocation followed by dimer interactions with specific DNA sequences in target genes, or modulates gene expression without direct DNA binding. The multiple distribution throughout the genome and interactions with transcription factors leads to a complex estrogen effect on gene expression. $ER\alpha$ increases the production of vasodilators such as prostacyclin and nitric oxide (NO) by upregulating endothelial NO synthase or by increasing intracellular calcium, a cofactor for endothelial NO synthase activity, reduces the production of vasoconstrictors such as endothelin and angiotensin, and reduces the oxidative stress and the pro-inflammatory cytokines [28], while $ER\beta$ modulates the expression of $ER\alpha$, antagonizes some of the beneficial effects of estrogens, and plays a role in central nervous system and heart. Recent studies have found that $ET\beta$ receptors are also located on the endothelium, and their blockade increase vasodilatory responses in postmenopausal women, demonstrating a loss of $ET\beta$ receptor-mediated dilation with aging/menopause.

One mechanism contributing to the impaired endothelial function following estrogen deficiency and aging is the oxidative stress that represents the production/destruction imbalance between the reactive oxygen species whose overproduction leads to NO suppression. E_2 also inhibits endothelin synthesis, an effect that after menopause would be lost with consequent increase of endothelin, a potent vasoconstrictor. Endothelin stimulates the oxidative stress and increases renal sodium reabsorption with consequent BP rise.

Moreover, some authors found that endothelin synthesis can be upregulated by angiotensin II, oxidative stress, and androgens [29]. Another mechanism contributing to endothelial dysfunction in menopause is the activation of the RAAS with reduction of E_2 . The RAAS controls the pressure–natriuresis relationship via angiotensin II that increases proximal sodium reabsorption by the kidney. E_2 downregulates the levels of angiotensin type I receptors and angiotensin-converting enzyme levels, thus protecting against the overproduction of angiotensin II and subsequent vasoconstriction. These beneficial effects of estrogen would be lost after menopause making many postmenopausal

women salt-sensitive. In hypertensive postmenopausal women, HRT was associated with a decrease in salt sensitivity, and treatment with angiotensin I receptor antagonists did improve endothelial dysfunction supporting a partial role for RAAS [30]. However, in normotensive postmenopausal women, transdermal E_2 reduced BP but had no effect on RAAS components. In summary, endothelial dysfunction, with reduction in vasodilators modulating vascular tone, may be one mechanism by which estrogen deficiency may result in high BP in postmenopausal women.

Using flow-mediated dilation (FMD), several studies demonstrated an impairment in endothelial function occurring with healthy aging, a decline that was faster in postmenopausal women [30]. Taddei [31] reported that, in response to acetylcholine, endothelium-dependent FMD was less attenuated with age in fertile hypertensive women than in men, while in postmenopausal women the FMD response was attenuated to the same extent than in men. However, HRT had no beneficial effect on FMD in postmenopausal women. It has been established that aging and estrogen deprivation are both associated with a reduction in NO bioavailability. Therefore, it is challenging to completely separate the effect of aging from the hormonal changes that occur with menopause.

The androgen hypothesis

Not only estrogen reduction but also androgen dysregulation has been supposed to influence BP in postmenopausal women. However, how androgens contribute to hypertension in postmenopause is unclear. Postmenopausal ovaries continue to secrete androgens, which, added to those of adrenal origin, exerts a pleiotropic effect on BP. In the Rancho Bernardo cohort, serum testosterone decreased at first with menopause, but increased with age thereafter, reaching premenopausal levels by age 70 to 79 [30]. Premenopausal women with polycystic ovary syndrome or virilizing tumors have elevated serum androgens and increase in BP.

Increased androgenicity may affect arterial stiffness via specific arterial wall androgenic receptors, increased vascular inflammation, endothelial dysfunction, deterioration of arterial wall elastin/collagen ratio and directly by inducing release of vasoconstrictor agents.

However, some of the studies supporting this hypothesis were biased by a retrospective approach. Assessing hypertension as a clinical endpoint, higher total testosterone concentrations were found in hypertensive than in normotensive women [32]. In patient-based data, high-testosterone hyperandrogenic women showed higher risk of hypertension. Furthermore, in female patients suffering from polycystic ovary syndrome associated with hyperandrogenemia,

a significant positive correlation between total testosterone and BP was observed even after adjusting for BMI. Ziemens et al. [33] observed a positive and independent association of total testosterone with BP that was consistent in cross-sectional and longitudinal analyses, while low testosterone was protective against hypertension (an evidence that was consistent both in premenopausal and in postmenopausal women). On the other hand, others showed that androgen deficiency was a major determinant of the increased prevalence of hypertension in postmenopausal women, adipocyte dysfunction being the main mechanism involved. The mechanism of the testosterone → BP interaction could be a sensitization of smooth muscle cells to constrictor stimuli leading to an amplification in myogenic tone, or endothelial dysfunction via activation of the RAAS [30]. Other studies found no association between androgens and BP, or inconsistent results.

The hypothesis of sympathetic drive

Evidence shows that the sympathetic nervous system is important in both short-term and long-term control of BP. Aging is associated with increased sympathetic nerve activity (SNA) leading to an increased risk of hypertension in older people. Now, it has been suggested that in healthy young men SNA variability is balanced by variability in cardiac output and in vascular adrenergic responses, BP remains as a consequence similar—and normal—across a wide range of resting SNA values. Muscle SNA correlates positively with total peripheral resistance and negatively with cardiac output, probably preventing healthy men with high muscle SNA from developing higher BP with growing old. On the contrary, in young women, the balancing mechanisms could be different in that, women could have a greater β -adrenergic vasodilation minimizing the pressor effects of a given level of SNA. So, young women with high levels of muscle SNA do not necessarily have, differently from men, high peripheral resistance [34]. And in fact, it has been shown that in young men but not in young women norepinephrine administered in the brachial artery leads to vasoconstriction.

Menopause adds an extra complication to the aging process; the rate of BP rise during menopause transition is much greater than that in men over the same age range. The described β -adrenergic mechanism that minimizes noreadrenergic vasoconstriction in young women disappears or becomes smaller in postmenopausal women.

The reason of this sex-specific difference is uncertain, although some answers come from animal studies. In rats, estrogen replacement in ovariectomized females restored the arteriolar dilatory β -adrenergic response to isoprenaline infusion, a response that is inhibited by β -blockade. The link between estrogen and vasodilation could be NO, also

considering that estrogen stimulates endothelial NO synthase increasing NO production. Unfortunately, both muscle SNA and BP increase with age, while estrogen decreases, making the analysis more complex and needing further confirmation.

The hypothesis of obesity

Prevalence of obesity reaches 40% in postmenopause, and has been shown to increase after surgical menopause or HRT. Even when postmenopausal women do not gain additional weight, there is a redistribution of fat to the abdomen [30]. Visceral adiposity is positively associated with testosterone production, free androgen index increase, and sex-hormone-binding globulin reduction. A given visceral adipose mass is also associated with a greater increase in muscle SNA than the same adipose mass of a different depot. Greater sympathetic activity increases renin release and angiotensin II formation, which in turn increases adrenal aldosterone production with resultant sodium retention.

Actually, BMI—which correlates with age and BP—is higher in postmenopausal women both in comparison to fertile women and to men even after age-adjustment [23]. More in general, postmenopausal women have, in comparison to fertile ones, worse lipidemia [13, 19] and greater gynoid adiposity, a phenotype also depending on genetic pattern and in particular on the GNB3 gene [13]: premenopausal women carrying the 835 T mutation show a lipidic and metabolic pattern similar to that of postmenopausal ones, being in this respect biologically older than their anagraphic age [13]. These differences are independent of BP and could explain the supposed greater propensity of postmenopausal women to metabolic syndrome and to cardiovascular events.

Clinical implications

In the light of literature and personal experience, a direct association between increase in the BP values (or in the rate of arterial hypertension) is not conclusively demonstrated. Many excellent pieces of research showed that BP is not affected by menopause, when correct statistics—such as matching women for age and BMI—are applied. If those two covariates have a causative role in the relationship between BP and menopause with a statistical meaning of determinants, or are a mere epiphenomenon with a statistical meaning of confounders, remains debatable. In other studies, menopause appeared to be, on the contrary, a determinant of high BP independent of age and adiposity.

Even accepting that BP is really higher in postmenopausal than in the premenopausal women, it appears

simplistic to attribute this to a mere estrogen drop accompanying menopause. Further research is needed to fully understand the role of intermediate phenotypes such as adiposity, age and endothelial dysfunction. The role of genetics is also unclear as menopause might provide a trigger for the expression of certain genetic influences that mediate high BP in women.

A collaboration between epidemiologists, clinicians, and experimental researchers is mandatory.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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