Is menopause an independent cardiovascular risk factor? Evidence from population-based studies

Edoardo Casiglia[a], Valérie Tikhonoff[a], Paolo Mormino[a], Antonio Piccoli[b] and Achille C. Pessina[a]

The question on whether menopause is an independent cardiovascular risk factor is still under debate. The results of four studies conducted by our staff in North East Italy, including > 11 000 subjects from the general population and covering a range of ages from 18 to 95 years, have been employed.

We found apparently higher blood pressure (BP) values in naturally menopausal than in fertile women, but this difference disappeared after age-correction, or after identifying fertile and menopausal age-matched women.

Significantly higher levels of serum lipids were also observed in menopausal than in fertile women but, in this case too, any difference disappeared after age-correction/matching.

In a 16-year longitudinal analysis we found that BP increase and incidence of hypertension were the same in the women who remained fertile, in those becoming naturally menopausal and in those already menopausal at baseline; going through the menopause period, therefore, has no effect on BP. A mild and transitory BP increase was only observed *during* the climaterium.

The BP increase during a follow-up and the incidence of new cases of hypertension were also similar in the women who remained fertile and in those who underwent bilateral ovariectomy, indicating no direct effect on BP for surgical menopause. In contrast, vectorial analysis demonstrated an excess increment of serum lipids among the women who underwent oophorectomy.

In our populations, menopause had no predictive role and was rejected from the multivariate equations of risk, cardiovascular risk being completely explained by age and BP (both higher in menopausal then in fertile women). *J Hypertens* 20 (suppl 2):S17–S22 © 2002 Lippincott Williams & Wilkins.

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[a]Department of Clinical and Experimental Medicine and [b]Department of Medical and Surgical Sciences, University of Padova, Padova, Italy.

Correspondence and requests for reprints to E. Casiglia, Department of Clinical & Experimental Medicine of the University of Padova, Via Giustiniani 2, I-35128 Padova, Italy.
Tel: +39 49 8212275; fax: +39 49 8754179; e-mail edoardo.casiglia@unipd.it

Introduction

Is menopause an independent cardiovascular risk factor? Is surgical menopause more dangerous than natural menopause? These questions are still under debate. Some authors found higher levels of arterial blood pressure (BP) [1] and serum lipids [1,2] in naturally menopausal women than in fertile women, other authors found no unfavorable effects of menopause [2–5]. The few longitudinal studies on natural menopause were unable to demonstrate any direct effect of the decreased ovarian function on cardiovascular mortality or morbidity [3], as well as on the development of arterial hypertension or hypercholesterolemia [3,4].

In this paper, three statements that are generally accepted acritically are discussed, namely that after menopause: (1) BP and vascular reactivity rise, (2) the lipid pattern worsens, and (3) mortality and morbidity also increase dramatically. To this aim, the results of four studies conducted in North East Italy [3,6–9], including more than 11 000 subjects from the general population and covering an age range from 18 to 95 years, have been employed.

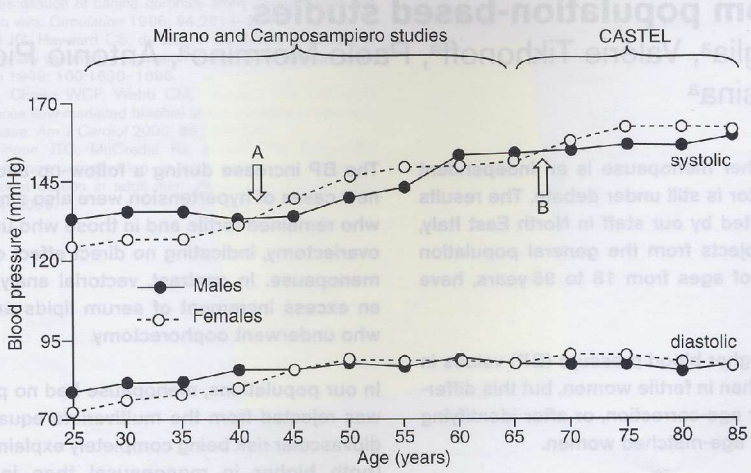
Natural menopause

Cross-sectional studies

Natural menopause is a condition that affects all women after the age of 50 years. If it is a risk factor, it must be one of the most widely diffused.

The belief that natural menopause increases BP derives from *BP versus age* curves (Fig. 1). BP (particularly systolic BP) is lower in women than in men in the first decades of life, and then there is a cross inversion (arrow A). This is an impressive pattern, as the age of the cross-inversion (around 50 years) is just that of the climaterium, which marks the beginning of estrogen decline. This pattern has been used to demonstrate that the sexual dimorphism is attenuated (even inverted) in menopause, to the point that the women's 'cardiovascular advantage' suddenly becomes a disadvantage after the climaterium.

Fig. 1



Cross-sectional population-based analysis ($n = 11\,067$). Trend of systolic blood pressure in a young Italian general population (Mirano and Camposmampiero studies, age < 65 years) [3,6] and in an elderly general population (CASTEL [7,8,10,11] and LEOGRA [9] studies, age ≥ 65 years) [7–11]. Arrow A indicates a significant ($P < 0.01$) cross-inversion usually considered as an effect of menopause; arrow B another significant ($P < 0.01$) cross-inversion, identical to A, occurring after the age of 70 years and therefore not due to menopause.

Table 1 **Blood pressure (BP) and lipid values in 108 fertile women aged 37 ± 9 years and in 381 menopausal women aged 52 ± 5 years [3]**

	Unadjusted values		Age-adjusted values	
	Fertile women	Menopausal women	Fertile women	Menopausal women
Systolic BP (mmHg)	132 ± 18	143 ± 24*	134 ± 20	133 ± 24
Diastolic BP (mmHg)	80 ± 12	87 ± 11*	82 ± 12	80 ± 14
TC (mg/dl)	199 ± 38	231 ± 42*	228 ± 32	222 ± 46
TG (mg/dl)	83 ± 42	106 ± 55*	98 ± 47	104 ± 56
Glucose (mg/dl)	93 ± 10	96 ± 18*	95 ± 10	95 ± 25

Both unadjusted and age-adjusted values are shown. TC, serum cholesterol; TG, serum triglycerides. A significant difference is present between fertile and menopausal women (*$P < 0.01$) but only when unadjusted values, irrespective of age, are employed.

In general, ages older than 60 or 65 are not taken into consideration by researchers who study menopause, simply because only a few researchers have data on the elderly general population.

When the elderly general population is considered [7–11], a pattern similar to that described for the younger population can be observed (arrow B). There is no scandal in stating that neither the cross-inversion A or the cross-inversion B is due to menopause, but simply to the dynamics of BP at a population level.

Another problem is age. It is known that in menopausal women the endogenous estrogen level decreases; age, on the contrary, increases substantially. A method able to distinguish the effects of hormonal changes from those of age is therefore needed.

Table 1 demonstrates the crucial importance of age. Among 568 women from the general population [3], menopause was apparently associated with a significant increase of both systolic BP (+8%, $P < 0.01$) and diastolic BP (+9%, $P < 0.01$). Nevertheless, menopausal women were 30% older than the fertile ones, and any difference between fertile and menopausal women disappeared after statistical correction for age. Age-matching is another (more powerful) way to abolish the confounding effect of age. In Table 2, 60 fertile and 60 age-matched menopausal women having the same mean age of 49.3 ± 5.3 years (identified with the case-to-case matching method [3]) were compared: the age being exactly the same in the two groups, no difference in BP was observed.

It has also been suggested that vascular reactivity could be higher after menopause, but with the cold pressor test (a hand in icy water for 1 min) we obtained [3] the same age-adjusted systolic pressor response in menopausal women (+15 mmHg) and in fertile women (+14.5 mmHg, insignificant difference). Other authors who observed a more pronounced response to mental stress in fertile women than in menopausal women did not correct the results for age [12].

Table 2 Blood pressure (BP) values among 60 fertile and 60 age-matched menopausal women of the same age (case-to-case matching)

	Fertile women aged 49.3 ± 5.3 years	Menopausal women aged 49.3 ± 5.3 years
Systolic BP (mmHg)	148.0 ± 21.0	143.6 ± 25.6
Diastolic BP (mmHg)	82.0 ± 12.5	79.6 ± 18.1

No significant difference between fertile and menopausal women (paired data *t* test).

Another open question is whether natural menopause worsens the lipid pattern. When our data were analyzed in this respect [3], significantly higher levels of serum cholesterol (+16%, $P < 0.01$) and triglycerides (+28%, $P < 0.01$) were apparently observed in menopausal women in comparison with those who were in the fertile status, but in this case too any difference disappeared after correction for age (Table 1). Lipids and glucose are, in fact, strictly related to age, and tend to increase with growing old.

Shelley *et al.* recently confirmed indirectly our opinion by demonstrating that lipids do not correlate with serum estrogen [13]

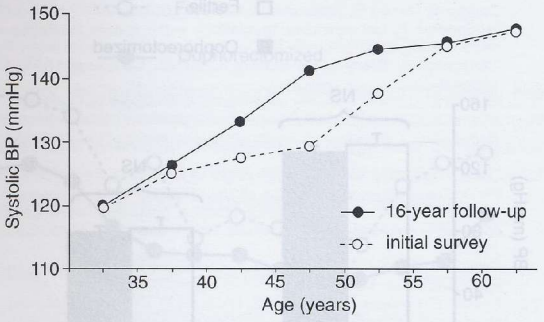
Longitudinal studies

Another way of investigating whether natural menopause modifies BP is the longitudinal approach. In a 16-year longitudinal analysis (Fig. 2), we found that the BP increase and the incidence of new cases of hypertension during the follow-up were the same in the women who remained fertile, in those who became naturally menopausal during follow-up, and in those who were already menopausal at baseline. Only a 16-year aspecific BP increase, comparable in the three groups and due to increasing age, was put in evidence. In our opinion, this demonstrates that going through menopause during a follow-up period has no effect on BP.

However, to be more precise, this is true for the stabilized women in the post-menopausal period.

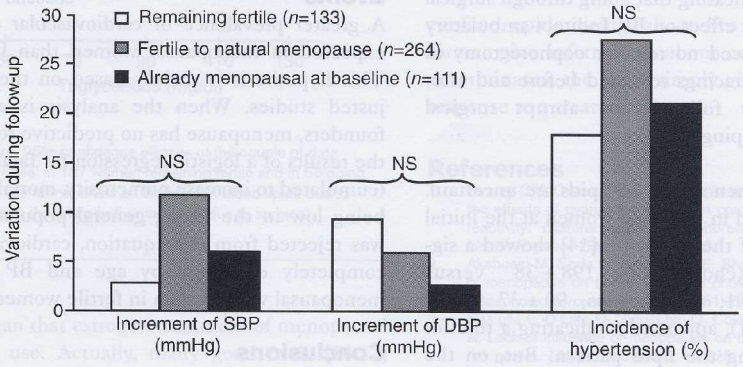
The hypothesis has been advanced that BP could increase *during* rather than *after* the climaterium. The way to investigate this is to compare the *age versus BP* curves obtained in two different occasions, i.e. at baseline and at the end of the follow-up. This is the case in Fig. 3, where the curves diverge at the age of 45–55 years, when climaterium typically occurs, perhaps demonstrating that climaterium increases BP.

Fig. 3



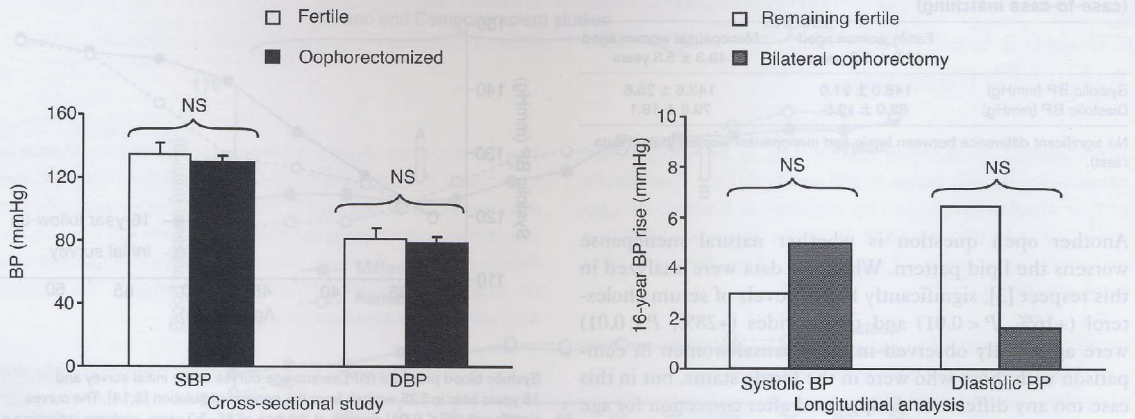
Systolic blood pressure (BP) versus age curves at the initial survey and 16 years later in 525 women from the general population [3,14]. The curves significantly ($P < 0.01$) diverge at the age of 45–50 years, perhaps indicating a role for climaterium in increasing systolic blood pressure.

Fig. 2



Longitudinal population-based analysis. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) increment and percent incidence of new cases of arterial hypertension during a 16-year follow-up of a general population [3]. No difference was evident between the women who remained fertile, those who became naturally menopausal during the follow-up and those who were already menopausal at baseline. NS, Not significant.

Fig. 4



Left panel: Blood pressure (BP) values (mmHg) among 441 fertile and 25 oophorectomized women [3]. Right panel: 16-year BP increment among 137 women who remained fertile and 56 who went thorough oophorectomy during the follow-up [3]. SBP, Systolic BP; DBP, diastolic BP; NS, insignificant difference.

This transient situation, provided it exists, disappears when women come out from the climacterium, reaching the more stable condition of full menopause. This is why BP is similar in fertile and post-climateric women, under the same conditions of age.

Surgical menopause

It has been suggested that the pressor effects of menopause could be more pronounced when menopause occurs suddenly (surgically), but this is not always true. In the left panel of Fig. 4, where fertile and bilaterally ovariectomized women have been cross-sectionally compared [14], the age-adjusted BP values were clearly the same. In the right panel, the BP increase during the follow-up, as well as the incidence of new cases of hypertension, were similar in the women who remained fertile and in those who underwent bilateral ovariectomy, indicating that going through surgical menopause has no direct effect on BP. Indirect ambulatory BP monitoring also showed no role for oophorectomy in increasing BP. The BP tracings recorded before and after bilateral oophorectomy followed by abrupt surgical menopause were overlapping (Fig. 5).

The effects of surgical menopause on lipids are uncertain. The paired data analyzed in the same women at the initial survey and at the end of the follow-up [14] showed a significant difference (cholesterol, 198 ± 38 versus 239 ± 40 mg/dl, $P < 0.001$; triglycerides, 90 ± 37 versus 112 ± 52 mg/dl, $P < 0.001$), apparently indicating a role for ovariectomy in modifying the lipid pattern. But, on the other hand, cholesterol and triglycerides measured at the end of the follow-up did not correlate with the years of surgical menopause, apparently indicating no role in modifying the lipid pattern for ovariectomy.

To clarify this point, vectorial analysis [14,15] was performed to compare the 95% confidence ellipses (intervals) of the couple of data 'cholesterol and triglycerides'. In Figure 6, the confidence ellipses obtained at the 16th year in the going through ovariectomy (dashed) and in those remaining fertile (clear) did not overlap, due to an excess increment of the couple of data 'cholesterol and triglycerides' in the former in comparison to the latter. The lipid pattern during the follow-up was therefore different in the two classes. In other words, the fertile → fertile women simply had a spontaneous increase of serum lipids due to growing old, while the fertile → oophorectomized ones had a greater increase. We can separate in this manner the vectorial components of age and ovariectomy.

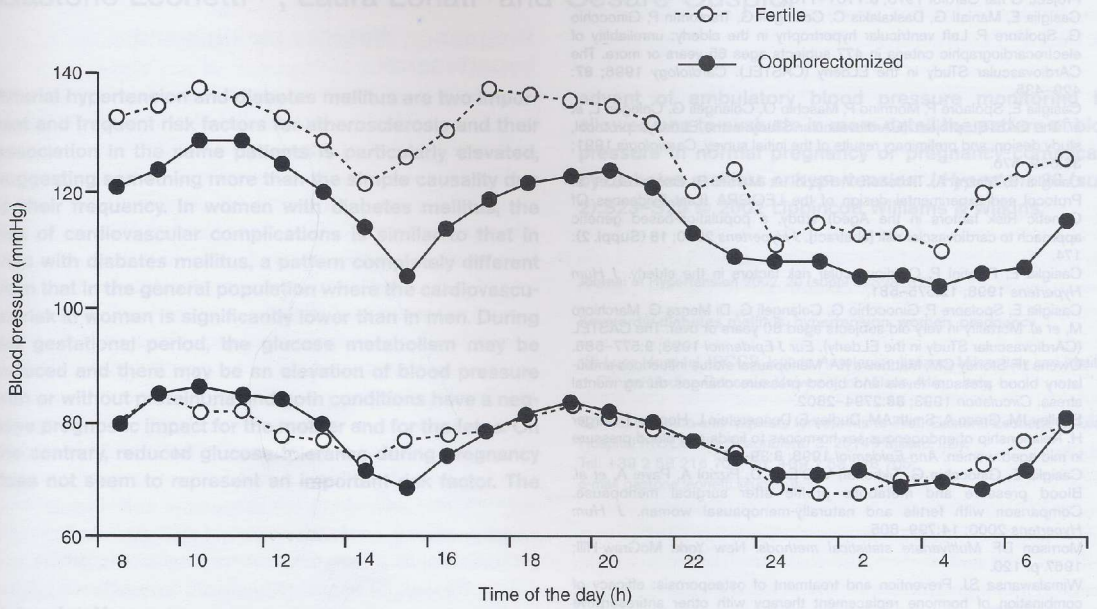
Events

A greater prevalence of cardiovascular events is usually expected in menopausal women than in fertile women. This hypothesis is mainly based on the results of unadjusted studies. When the analysis is adjusted for confounders, menopause has no predictive role. Table 3 shows the results of a logistic regression for fatal + morbid events (cumulated to increase numerosity, mortality and morbidity being low in the young general population). Menopause was rejected from the equation, cardiovascular risk being completely explained by age and BP (both higher in menopausal women than in fertile women).

Conclusions

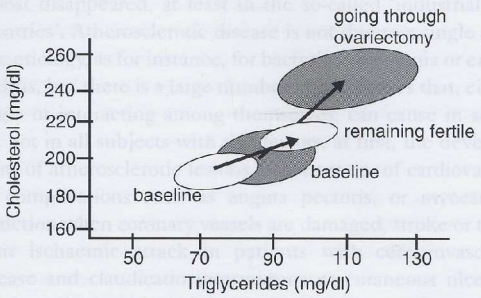
Our data suggest that one must be prudent before accepting that menopause worsens the cardiovascular risk pattern; in some cases, this opinion comes from inadequate studies, or it is not supported by numbers.

Fig. 5



Indirect ambulatory blood pressure monitoring ($n = 20$), showing that 24-h blood pressure values and 24-h blood pressure trends are comparable before ovariectomy (fertile status) and 6 months after bilateral ovariectomy (surgical menopause). Analysis of variance for repeated measures, no significant difference between the two curves.

Fig. 6



Vectorial analysis showing 95% confidence ellipses of the couple of data 'cholesterol and triglycerides' in 137 women remaining fertile and in 56 going through oophorectomy. The former show an increase of blood lipids due to increasing age; in the latter there is a further increase due to surgical menopause.

Table 3 Logistic regression for cumulated fatal + morbid events among 568 women of the general population [3]

Independent variables	χ^2 to remove	*P* value
Age (years)	4.26	0.0003
Systolic blood pressure (mmHg)	2.95	0.004
Diastolic blood pressure (mmHg)	2.61	0.007
Menopause (present, absent)	–	0.4 (not significant)

Menopause was rejected from the model.

This does not mean that estrogen treatment of menopausal women is of no use. Actually, many good trials [16,17] demonstrated that estrogen treatment is useful for reducing osteoporosis and perhaps cardiovascular disease. This could simply be due to aspecific effects and does not imply that menopause is a risk factor. It is very important not to confuse epidemiological studies with clinical trials: the former give information about cardiovascular risk and its determinants, the latter simply give information about the response to a treatment.

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