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Pulse pressure and age at menopause

Riitta Luoto*[1,2], A Richey Sharrett[1], Marsha Eigenbrodt[3] and Donna Arnett[4]

Address: [1]NHLBI, NIH, Two Rockledge Centre 6701 Rockledge Drive, MSC 7934 Bethesda, 20892, USA, [2]Tampere School of Public Health 33014 University of Tampere, Finland, [3]Department of Epidemiology, School of Public Health University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, USA and [4]Division of Epidemiology, University of Minnesota 1300 South Second Street, Suite 300, Minneapolis, MN 55454-1015, USA

E-mail: Riitta Luoto* - riitta.luoto@uta.fi; A Richey Sharrett - SharretR@nhlbi.nih.gov;
Marsha Eigenbrodt - meigenbrodt@HealthyArkansas.com; Donna Arnett - arnett@epi.umn.edu
*Corresponding author

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Abstract

Background: The objective of this study was to study the association of early age at menopause with pulse pressure (PP), a marker of arterial stiffness, and PP change.

Methods: The effect of natural menopause was studied in 2484 women from the Atherosclerosis Risk in Communities (ARIC) Study who had not used hormone replacement therapy and who had not had a hysterectomy. The cross-sectional association of age with PP was evaluated in the entire cohort. The cross-sectional association of recalled age at menopause was evaluated in the 1688 women who were postmenopausal at baseline. PP change over 6 years was assessed in relation to menopausal age separately in women who were postmenopausal at baseline and in those whose menopause occurred during the 6-year interval.

Results: Chronological age was strongly and positively associated with PP in cross-sectional analyses, but not independently associated with PP change. While menopausal age was not associated cross-sectionally with PP, early age at menopause (age<45) was significantly and independently associated with a slightly larger increase in PP (8.4, 95% CI 7.0–9.8) than later menopause (6.5, 95% CI 5.8;7.2). However, among normotensive women the difference was not statistically significant (p = 0.07, 6.1 vs 4.7).

Conclusions: Early age at menopause may be related to a greater increase in arterial stiffness, but the effect appears to be small and further evidence is needed.

Background

Pulse pressure, i.e. the difference between systolic (SBP) and diastolic blood pressure (DBP), is a crude but readily acquired measure of arterial stiffness. Recent findings from the Framingham study have suggested pulse pressure being superior to SBP and DBP in predicting CHD risk [1]. Increased arterial stiffness has been proposed as a marker or mechanism for initiation or progression of atherosclerosis and/or structural arterial changes due to hypertension [2]. Arterial stiffness estimated with ultrasound measured arterial diameter change, adjusted for blood pressure, was found to be higher in boys and men than in girls or women up to the age of 50–54 years, whereas these differences disappeared thereafter [2,3]. Menopausal factors, or loss of ovarian function, have been proposed to close the gap of the gender difference in arterial

stiffness after age 50. Early menopause may hasten the increase in arterial stiffening with age, and lead to an increased risk of cardiovascular mortality. A Dutch study showed a 2 % decrease in cardiovascular mortality associated with each year's delay in menopause [4]. A Norwegian study estimated a substantial protective effect of late menopause, with 60% fewer cardiovascular deaths among women reaching menopause at age 47 years or later [5].

In the current study we hypothesized that early age at menopause is associated with increased arterial stiffness as indicated by pulse pressure and with increasing pulse pressure over time.

Material and methods

The ARIC Study [8] is a prospective study of 15,792 45–64 year old men and women in four US communities: Forsyth County, North Carolina; Jackson, Mississippi; selected suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Initial participant response rates were 46% for Jackson and 66% for other three communities. The baseline examination of the ARIC study was conducted in 1987–89, and follow-up examinations occurred in 1990–92 and 1993–95. At the baseline, sitting blood pressure, anthropometry, venipuncture (12-hour fasting) and interviews concerning medical and reproductive history and medication use were performed. The accuracy of information pertaining to medication use was enhanced by asking the participants to bring containers of all medications used in the previous two weeks to the ARIC clinic to be transcribed by interviewers.

Three sitting blood pressure readings were recorded after 5 minutes of rest using a random zero sphygmomanometer. The systolic and diastolic blood pressure values used in the analysis as outcomes were averages of the second and third readings.

The total population at baseline included 8710 women. Women were classified as pre-, peri- or postmenopausal at baseline. Premenopausal women were those who reported that they had menstrual periods in the past 2 years, and had not reached menopause, or who reported no missing periods during last 2 years. Perimenopausal women were defined as those who reported that they had reached menopause but also reported any menstrual periods in the past 2 years. Women were defined as naturally postmenopausal if they had not been menstruating for the past 2 years and reported their menopause was natural. Similar menopausal definitions have been applied and described in earlier ARIC studies [6,7].

We excluded 686 women with unknown menopausal status at any visit, 21 women of ethnic origin other than African-American or white, 548 women with missing information on 3-year and/or 6-year follow-up, 2765 women who had ever used hormonal replacement therapy (HRT), 302 women coded as perimenopausal at both baseline and 6-year follow-up or those who underwent hysterectomy during the follow-up and 588 women who had missing values for other analysis variables. All women who had undergone hysterectomy prior to baseline (N = 1316) or during follow-up were excluded leaving 2484 women in the study population. The rationale for excluding women who had ever used HRT, those who had a hysterectomy, and those who remained perimenopausal at the end of the study, was to study the effect of untreated natural menopause. A greater proportion of women in the excluded sample were black, fewer had a high school education, and fewer had used antihypertensive medications than women in the included sample.

In the final study sample, age at natural menopause was reported at baseline by 1,688 postmenopausal, non-hysterectomized women. Since there might be differences by the centers in the time between follow-up visits and other factors, adjustments by ARIC field center were performed by using three dummy variables in most of the models.

Because pulse pressure is affected by hypertension per se and hypertensive medication, we divided women into consistent users of hypertensive medication and all others. Consistent users included women who reported hypertensive medication use at baseline and each follow-up visit.

Chronological age was evaluated in the entire study population (2484 women) in relation to PP level at baseline and at the 6-year follow up examination (cross-sectional analysis) and also in relation to the 6-year change in PP (longitudinal analysis). Both PP level and PP change were studied similarly in relation to recalled age at menopause in the 1688 women who were menopausal at baseline. Finally, PP change was analyzed in relation to recorded age at menopause in the 259 women who underwent menopause between the baseline examination and the 6-year follow up examination.

In order to adjust the 6-year change in pulse pressure for confounding factors, analysis of covariance was performed. Pulse pressure change was the dependent variable; age at menopause was the independent variable and baseline age, baseline pulse pressure, race, hypertensive medication use, ARIC field center and smoking were the covariates considered.

When fitting by ordinary techniques models of change in an outcome variable as a function of some exposure and the baseline level of the outcome variable, it is well known that the presence of measurement error in the baseline

outcome variable can cause substantial bias in the estimates of all model coefficients [9]. One method to correct the measurement error is to replace the baseline values of the outcome variable by Stein estimates of the true values of that variable, and then apply ordinary least squares [9]. In correcting for measurement error we have used estimates for repeatability of SBP, DBP and PP from a sample of 363 ARIC female participants with repeat measurements 1–2 weeks apart during ARIC visit 3. The correlation coefficients for repeat measurements of SBP, DBP and PP were 0.75, 0.62 and 0.66, respectively.

Due to the possibility of varying prevalence of hypertensive subjects in different age-groups to confound pulse pressure change estimates, we also studied PP change as % from baseline. Secondly, we considered the possibility of age at menopause being significant variable when using it as continuous in the multivariate models. Thirdly, formal analyses to consider potential interaction between hypertension status at baseline or use of hypertensive medication and menopausal age have been performed also.

Results

Among the women who were postmenopausal at baseline, there was no cross-sectional association of pulse pressure with recalled age at menopause (Table 1). Longitudinally, the 6-year increase in PP was greatest among those who had undergone menopause at the earliest age, 25 to 35 years, though the overall linear trend was not statistically significant. Women recalling their menopausal age as younger than 45 years had a significantly higher PP increase (8.0) than women recalling their menopausal age as 45 years or older (6.6), after adjusting for age at baseline, baseline PP, race and hypertensive medication use. PP change for earlier (< 45 years) menopausal women was significantly (p = 0.014) higher (8.4) than PP change for women menopausal at age 45 or older (6.5) after taking into account measurement error. However, among normotensive women the difference was not statistically significant (p = 0.07, 6.1 vs 4.7). Age at menopause was also used as continuous variable in the models explaining pulse pressure change, but it was not significant.

When pre- or perimenopausal women at least 45 years of age at baseline were followed for 6 years, those with lower estimated age at menopause did not have greater PP increase over time compared to women with higher estimated age at menopause (Table 2).

In the cross-sectional analyses, at baseline and at the 6-year follow-up, systolic blood pressure was strongly positively associated with chronological age, but diastolic BP varied little with age (Figure 1). Thus, the difference between SBP and DBP, i.e. pulse pressure, increased with age. In the baseline data, average pulse pressure was 42.3 mmHg in women aged 45 to 46 years and increased monotonically to 56.5 mmHg in the oldest women aged 62–64 years (Table 3). Linear trends in both cross-sectional associations between baseline age and baseline PP as well as between baseline age and PP at 6-year follow-up, were highly significant (p=.0001) even after adjusting for race and hypertensive medication use. Longitudinally there was a significant relationship (p=.0001) between 6-year change in pulse pressure and chronological age at baseline after adjustment for baseline PP, race, hypertensive medication use, ARIC field center and smoking (Table 1). This relationship did not remain significant after additional adjustment for measurement error (p = 0.23).

The proportional changes in pulse pressure were nearly similar in both hypertensive and non-hypertensive subjects, but the absolute values differed. The different prevalence of hypertensive subjects in age-groups did not explain the results. Additionally, the interactions between hypertensive status at baseline or use of hypertensive medication and menopausal age were not significant in any subgroup, with or without adjustments for other variables (results not shown in tables).

Discussion

Pulse pressure, a marker of arterial stiffness, is clearly related to older chronological age. Our study suggests that PP may also be related to older "biological age", if one considers early age at natural menopause as a sign of biological aging. Women whose menopause occurred before age 45 experienced a greater increase in PP than women with menopause at later ages. This association remained significant when taking into account chronological age, baseline PP, race, and use of antihypertensive medications. However, the association was limited to PP change and was not seen for PP level at baseline or 6-years later. The PP effect appears to be slight in magnitude, approximately 2 mm Hg, so it may be detected better in longitudinal than cross-sectional analyses. Longitudinal analysis reduces the effects of extraneous variables, since each woman serves as her own control when her baseline PP is subtracted from her 6-year PP. Furthermore there was no association of PP with later menopause, suggesting that age at menopause after age 45 is not an effective marker of biological aging. Arterial stiffening, as assessed by pulse pressure, may offer one explanation for the findings of others relating cardiovascular risk to menopause before age 45[4,5].

A change in PP in relation to menopause could reflect the gradual reduction in circulating sex hormones which occurs at the time of menopause. However, our earlier findings provide some evidence against that interpretation [7]. There we showed that women currently undergoing the menopausal transition had no more perimenopausal

Table 1: Systolic (SBP) and diastolic (DBP) blood pressure, pulse pressure (PP) and PP change by recalled age at menopause among non-hysterectomized women postmenopausal at baseline. N = 1688.

			Baseline			6-year follow-up					
Recalled age at menopause	N	Mean age at baseline	SBP	DBP	PP	SBP	DBP	PP	PP change	Adj[1] PP change	95% CI
25–35	40	57.6	122.9	72.3	50.6	129.5	68.4	61.1	10.5	10.1	6.1–14.2
36–40	155	56.8	122.2	71.1	51.1	128.9	69.5	59.4	8.3	8.7	6.6–10.7
41–44	167	56.5	118.9	70.3	48.6	124.5	68.5	56.0	7.4	7.3	5.3–9.3
45–48	501	57.0	123.1	71.9	51.2	127.3	69.7	57.5	6.3	6.6	5.5–7.8
49–51	469	58.1	123.4	71.7	51.7	128.1	70.0	58.1	6.4	6.2	5.0–7.3
52+	356	59.8	125.4	71.3	54.0	129.9	68.7	61.2	7.2	6.8*	5.4–8.2

[1] Adjusted for baseline age, baseline PP, race, hypertensive medication use and measurement error. * Adjusted test for linear overall trend p = 0.20, for women menopausal at age <45 (PP change 8.4, 95% CI 7.0–9.8) vs. age = 45 (PP change 6.5, 95% CI 5.8–7.2), p = 0.014.

Table 2: Systolic (SBP) and diastolic (DBP) blood pressure, pulse pressure (PP) and PP changes by estimated age of menopause. N = 259. Only women pre- or perimenopausal at baseline included.

			Baseline			6-year follow-up					
Estimated age at menopause	N	Average age at baseline	SBP	DBP	PP	SBP	DBP	PP	PP change	Adj.[1] PP change	95% CI
45–50.4	151	47.8	115.8	71.7	44.1	121.4	71.6	49.7	5.7	5.7	3.4–8.0
50.5–52.4	43	49.1	117.1	71.9	45.2	125.3	73.2	52.1	6.8	6.5	2.7–10.4
52.5–54.4	37	50.3	117.8	72.5	45.3	122.9	73.4	49.5	4.2	4.1	-0.2–8.4
54.5–65.5	28	52.0	123.2	74.4	48.8	128.3	73.6	54.7	5.9[2]	6.7[3]	1.3–12.1

1 Adjusted for baseline age, baseline PP, race, hypertensive medication use and ARIC field center. 2 Test for overall linear trend p = 0.87. 3 Test for overall linear trend p = 0.74.

change in BP than women of the same age not undergoing the transition. Our current findings are different. They show a greater PP increase after a baseline examination in women who recalled their menopausal age as younger than 45 years compared with similar women with later menopausal ages. We interpret this postmenopausal PP increase as suggesting that early menopause may be an indicator of a more rapid biological aging process, i.e. that women with an early menopause are generally aging more quickly than expected for their chronological age, as evidenced by the relatively rapid changes in arterial stiffness observed postmenopausally. Earlier studies have shown that estrogen deficiency may induce functional changes in large arteries, but structural changes are more likely to be seen in long-term effects [10–15].

Ours is *not* the first study to evaluate the effect of menopausal age on pulse pressure, a surrogate marker for arterial stiffness, which may serve as an indicator of preclinical atherosclerosis. Menopause per se has been shown to be associated with increasing stiffness of the aorta, later leading to dilatation of the common carotid artery [16]. Most earlier cross-sectional studies during the 1990's, which have addressed the relations between timing of menopause, mortality, cardiovascular mortality and myocardial infarction, have shown significant association between age at menopause and cardiovascular outcomes [4,5,17,18]. Among Seventh-Day Adventists, age-adjusted OR of death in women with natural menopause before age 40 was 1.95 (95% CI 1.24–3.07), and the OR decreased with increasing age at natural menopause until

Table 3: Pulse pressure (PP) and PP changes by chronological age at baseline among non-hysterectomized women. N = 2484.

Age at baseline	N	Adjusted PP at baseline[1]	Adjusted PP at 6-year follow-up[1]	AdjustedPP change[2]	Adjusted PP change corrected for measurement error[3]	95% CI
45–46	206	42.3	47.4	5.1	6.2	4.5–8.0
47–49	266	44.0	48.7	4.7	5.2	3.6–6.7
50–52	364	45.9	51.1	5.3	5.4	4.1–6.7
53–55	398	48.2	53.5	5.3	5.1	3.9–6.4
56–58	442	50.6	57.6	7.0	6.6	5.5–7.8
59–61	418	53.7	61.0	7.2	7.0	5.8–8.3
62–64	390	56.5[1]	64.1[2]	7.6[3]	7.3	6.0–8.6

[1] Test for overall linear trend, adjusted for race and hypertensive medication use, p = 0.7149 [2] Test for overall linear trend, adjusted for baseline PP, race, hypertensive medication use, ARIC field center and smoking, p = 0.64 [3] Additionally corrected for measurement error, p = 0.23.

age 55[17]. In two studies, cardiovascular mortality has been found to be greater in women with age at menopause lower than 45 years as compared to women with later age at menopause [4,5]. One recent study reported slightly increased risk of total mortality (adjusted mortality rate ratio 1.50, 95% CI 0.97–2.34) among women with a natural menopause at age 40 or before as compared to women who were menstruating to age 50 or later [18]. Spontaneous cessation of ovulatory function before age 45 was associated with increased risk of myocardial infarction (RR 2.1, 95% CI 1.3–3.2) as compared with women who had a natural menopause at age 50 or older [19]. In Nurses' Health Study, age at menopause lower than 35 years was associated with increased risk of myocardial infarction, but natural menopause at later ages was not [20].

Earlier longitudinal studies [21–25] have addressed the question of menopause and hypertension as well. According to the Framingham study menopause was not accompanied with changes in blood pressure [21]. In a Swedish and Pittsburgh cohort studies [22,23] the findings correlated Framingham study results. A Dutch cohort including a selected sample of women also concluded that menopause is not a possible cause of hypertension [24,25], although ovarian failure seemed to reverse temporarily the increase in blood pressure due to aging. In a recent longitudinal study by Scuteri et al [26], postmenopausal women using HRT had a smaller increase in systolic blood pressure than women not using HRT.

Opposite to the findings of longitudinal studies, a large number of studies measuring either diameter, compliance, distensibility of large arteries or aortic pulse wave velocity have concluded that menopause per se is associated with loss of aortic elasticity, over and above the effects of aging [27–33].

On the basis of studies using other measurements described above, there are limitations in the use of pulse pressure as an index of stiffness. Pulse pressure is determined by a number of factors apart from arterial stiffness including heart rate, stroke volume, and ejection time. Results might have been different with a more sensitive measurement of arterial stiffness. Studies, which have assessed menopause and arterial stiffness using carotid ultrasound measurements, provide some support for our findings, although the relationship between *timing* of menopause and change in stiffness was not assessed in any of the described studies [34–37]. Stiffness was found to be significantly greater in postmenopausal than age-matched premenopausal women in the Dutch study [34]. Menopause had an independent significant association to the stiffness index in the Swedish study [35]. In the Healthy Women Study from Pittsburgh [36] premenopausal values of pulse pressure were independently predictive of plaque.

Since the ARIC cohort was limited to persons aged 45 or older, our findings relating to menopause before age 45 had to depend on recall, which may be imprecise. Recall errors may increase with time from the menopause [37], but appear not to be related to educational status or age at interview [38]. Imprecision in recalled age at menopause may have attenuated our findings somewhat.

Factors known to be associated with early age at menopause are smoking [39,40], low sociodemographic status [41], nulliparity [42,43] and leanness [44], although the effect of the latter may be partlyexplained by larger proportion of smokers among lean women. In our study, smoking did not explain the association between early age at menopause and pulse pressure change. Multiple triggers are known to lead to reproductive decline, but there is no consensus about an ultimate pacemaker of the men-

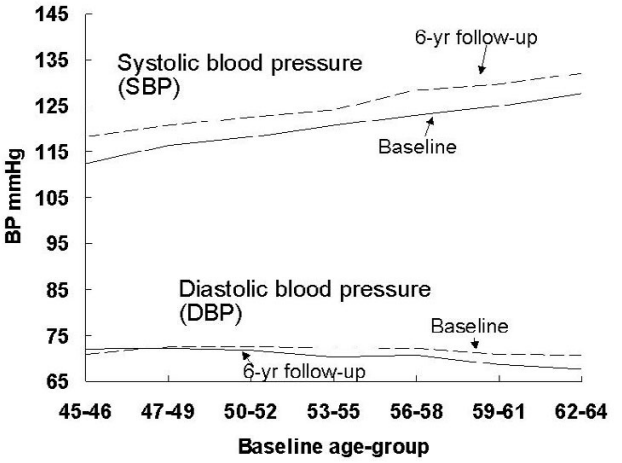

Figure 1
Systolic (SBP) and diastolic (DBP) blood pressure at baseline and 6-year follow-up visits by chronological age at baseline among non-hysterectomized women without HRT.

opausal transition [45]. One view maintains that the hypothalamic-pituitary changes that accompany menopause are a consequence of compromised ovarian function, whereas another view emphasizes age-related changes in the nervous system as initiators of menopausal transition [42]. Our study suggests that, whatever the reasons for early age at menopause, it appears to be independently and significantly related to a small subsequent increase in PP, but clearly, confirmation of this interesting finding is required.

Competing interests
None declared.

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