

Early Menopause, Number of Reproductive Years, and Bone Mineral Density in Postmenopausal Women

ABSTRACT

Objectives. Previous studies have reported positive associations of age at menopause with bone density and inverse associations of age at menarche with bone density. This study examined the relationships of early age at menopause and number of reproductive years (defined as age at menopause minus age at menarche) with bone density in postmenopausal women.

Methods. The subjects were 555 women aged 60 to 89 years who had had either natural menopause (n = 391) or hysterectomy with bilateral oophorectomy (n = 164). Bone density was measured at the ultradistal wrist, midshaft radius, lumbar spine, and hip.

Results. Women who had had early menopause and those with the fewest reproductive years had significantly lower bone density at all sites. After adjustment for covariates, both age at menopause and number of reproductive years had significant positive associations with bone density at every site, and total number of reproductive years explained more of the variance in bone mineral density than did either age at menarche or age at menopause.

Conclusions. Elderly women reporting early menopause or fewer reproductive years have more osteoporosis. The number of reproductive years may be more helpful than age at menopause in identifying women at increased risk of osteoporosis. (*Am J Public Health.* 1993; 83:983-988)

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Introduction

Age at menopause has been found to have a positive association with bone mineral density.¹⁻⁴ Many, if not most, women have a rapid phase of bone loss at the menopause, followed by a protracted period of slower bone loss that probably continues into old age.¹ However, it is not known whether osteoporosis in old age is greater in women who had a relatively early menopause than in those whose menopause was later. In other words, does the early osteopenia of estrogen deficiency at an earlier than average age at menopause carry a long-term penalty?

In contrast to results of studies on age at menopause, several studies have reported an inverse association of age at menarche with bone mineral density⁵⁻⁹ and risk of osteoporotic fracture.^{10,11} Number of reproductive years, defined as the years between menarche and menopause, simultaneously takes into account a woman's standing on both of these dimensions. However, there have been few studies that have examined the association between number of reproductive years and bone mineral density. Melton et al.¹² reported that the duration from menarche to menopause was significantly and positively associated with bone mineral density of the lumbar spine but not with bone mineral density of the cervical and intertrochanteric regions of the femur, the proximal femoral shaft, the midradius, or the distal radius. Vico et al.¹³ also reported a positive association of reproductive years with lumbar bone density but did not examine other sites.

The purpose of the present study was to examine the associations of age at menopause and number of reproductive years with bone mineral density at ultradistal wrist, radius, spine, and hip in a community-based sample of older, postmenopausal women.

Methods

Study Population

Between February 1988 and April 1991, 742 women aged 60 to 89 years from a White, upper-middle-class Southern California community (Rancho Bernardo) participated in a study of osteoporosis. These women were all enrolled in the Rancho Bernardo Heart and Chronic Disease Survey between 1972 and 1974 and have been followed ever since. All subjects were ambulatory and gave written informed consent. Women who had undergone a hysterectomy without a bilateral oophorectomy (n = 186) and the 1 woman who had never menstruated were excluded, leaving 555 women who were at least 5 years post menopause for the analysis of the relation of timing of menopause to bone density. Of these women, 391 had had a natural menopause and 164 had had a hysterectomy with bilateral oophorectomy. To avoid potential confounding of altered endogenous endocrine states leading to oophorectomy, analyses of the relation of reproductive years to bone density included only the 391 women who had had natural menopause.

Data Collection

A standardized interview was used to obtain information on smoking history, use of contraceptive and noncontraceptive estrogen and thiazide medications,

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TABLE 1—Age-Specific Characteristics of Postmenopausal Women^a Studied for Osteoporosis, Rancho Bernardo, Calif, 1988 through 1991

	60–69 y (n = 155)		70–79 y (n = 217)		80–89 y (n = 183)		F ^b
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Body mass index, kg/m ²	25.3	(4.3)	24.1	(3.9)	23.8	(3.6)	7.09*
No. reproductive years ^c	35.7	(5.8)	35.2	(6.2)	34.3	(5.7)	1.72
Age at menarche, y	12.7	(1.3)	13.2	(1.5)	13.5	(1.4)	12.33*
Age at menopause, y	47.8	(5.9)	48.0	(6.4)	47.4	(5.6)	0.46
No. years postmenopausal	18.1	(6.7)	27.3	(7.0)	36.0	(6.1)	308.25*
No. pregnancies	2.8	(1.8)	1.7	(1.7)	1.4	(1.4)	31.13*
Ever used oral contraceptives, %	25.8	...	3.2	...	0.5	...	81.04*
Ever used estrogen, %	77.4	...	72.8	...	65.0	...	6.61**
Currently use estrogen, %	49.0	...	33.6	...	18.0	...	36.71*
Bilateral oophorectomy, %	29.7	...	33.2	...	25.1	...	3.08
Use thiazide, %	8.4	...	10.6	...	8.2	...	0.85
Ever smoked, %	61.3	...	52.5	...	39.3	...	16.69*
Wrist BMD, g/cm ²	0.247	(0.092)	0.213	(0.089)	0.183	(0.090)	20.83*
Radius BMD, g/cm ²	0.644	(0.089)	0.568	(0.099)	0.526	(0.100)	59.79*
Spine BMD, g/cm ²	0.921	(0.160)	0.874	(0.189)	0.845	(0.190)	6.66*
Hip BMD, g/cm ²	0.841	(0.131)	0.765	(0.135)	0.703	(0.137)	42.82*

Note. BMD = bone mineral density.
^aMean age = 75.4 years (SD = 7.3) for all women and 75.6 years for the 391 women with natural menopause.
^bComparisons were performed with analysis of variance for continuous variables and chi-square analysis for categorical variables.
^cNumber of reproductive years was calculated as age at menopause minus age at menarche. The range was 8 to 49 years. The number of reproductive years is presented only for the 391 women with natural menopause. Mean number of reproductive years for all women by age-specific groups was 35.1, 34.8, and 34.0 for women aged 60–69, 70–79, and 80–89, respectively; F = 1.71, not significant.
*P < .001; **P < .05.

and reproductive and menstrual histories. The women were questioned about the number of pregnancies they had had and their age at menarche. Age at menopause was defined as age at the last menstrual period and number of reproductive years was defined as the difference between age at menopause and age at menarche. Height and weight were measured with the participant in light clothing and without shoes. Body mass index (weight [kg]/height [m]²) was used as an estimate of obesity.

Bone mineral density was measured at the lumbar spine and hip by dual-energy x-ray absorptiometry (Hologic QDR model 1000, Waltham, Mass) and at the midshaft of the radius and ultradistal wrist of the nondominant arm by single-photon absorptiometry (Lunar model SP2B, Madison, Wisc). The precision errors of these methods of measurement are 7.0% for the ultradistal wrist, 5.0% for the midshaft radius, 1.0% or less for the spine, and 1.5% or less for the total hip. Bone mineral density was defined as the average of the four contiguous lines that yielded the lowest mean bone mineral density at the ultradistal wrist site; as the average of four lines at the 33% midshaft radius site; and as the average of lumbar vertebrae 1 through 4 for the lumbar spine. For the hip, the tro-

chanter, intertrochanter, and femoral neck were evaluated separately; patterns of associations were similar but weaker at the individual sites, reflecting the lower stability of these estimates.¹⁴ Only the total hip bone mineral density (sum of the average bone mineral densities of the trochanter, intertrochanter, and femoral neck) is shown. Among the 555 women included in the analysis of timing of menopause, 555 bone mineral density measurements were available for the ultradistal wrist, 524 for the midshaft radius, 548 for the spine, and 541 for the hip. Among the 391 women included in the analysis of reproductive history, 391 bone mineral density measurements were available for the ultradistal wrist and hip, 370 for the midshaft radius, and 385 for the spine. Missing values represent subject fatigue, downtime for the scanner, or other technical difficulties.

Statistical Analysis

Histograms and quantile-quantile¹⁵ plots indicated that bone mineral density measurements were sufficiently normally distributed not to require transformation. Unadjusted means of bone mineral density at each of the sites measured and unadjusted means or proportions for the other measured variables were calculated

by 10-year age groups. Comparisons by 10-year age groups were accomplished by analysis of variance for the continuous variables and chi-square analyses for the categorical variables. The average age at menopause (47.8 years) was used to dichotomize the women into early and late menopause categories. Unadjusted comparisons between the early and late menopause groups were computed with *t* tests for continuous variables and chi-square analyses for categorical variables. Unadjusted comparisons by number of reproductive years (less than 30, 30 through 39, and 40 or more) as a categorical variable were calculated with analysis of variance for continuous variables and with chi-square analyses for categorical variables. Age-adjusted and other multiply-adjusted comparisons of bone mineral density at each site by timing of menopause and by number of reproductive years were computed by analysis of covariance. Separate hierarchical multiple regression analyses were used to examine the relationships of age at menopause and number of reproductive years as continuous variables to bone mineral density at each site measured, after adjustment for the potentially confounding covariates of age, obesity, parity, postmenopausal estrogen use, past oral contraceptive use, thiazide use, and cigarette smoking. In addition to these covariates, multiple regression analyses examining the association of age at menopause with bone mineral density also adjusted for bilateral oophorectomy. All statistical tests were two-tailed.

Results

The average age of these 555 women was 75.6 years. Age at menopause ranged from 21 to 62 years, with an overall mean of 47.8 years (including the 164 women who reported hysterectomy with bilateral oophorectomy). Among women who had had a natural menopause, average age at menopause was 48.2 years; among women who had had a hysterectomy with bilateral oophorectomy, average age at menopause was 46.8 years. Among women who had had a natural menopause, number of reproductive years ranged from 8 to 49, with a mean of 35.0 (SD = 5.9) and a median of 36.

Table 1 shows bone mineral density and other characteristics by 10-year age groups. Older women had significantly lower bone mineral densities at all sites. Neither age at menopause nor number of reproductive years varied significantly by age, but older women reported a later age

TABLE 2—Comparison of Covariates by Timing of Menopause and Number of Reproductive Years, Women Aged 60–89 Years, Rancho Bernardo, Calif, 1988 through 1991

	Timing of Menopause (n = 555)			No. Reproductive Years (n = 391)			F or χ^2
	Early (n = 226)	Late (n = 329)	t or χ^2	<30 (n = 70)	30–39 (n = 246)	≥40 (n = 75)	
Age, y	75.8	75.1	1.13	76.1	75.9	74.2	1.71
Body mass index, kg/m ²	24.3	24.4	0.30	23.9	24.3	25.0	1.44
Age at menarche, years	13.1	13.1	0.14	13.7	13.3	12.4	18.47*
Age at menopause, years	42.0	51.7	30.45*	39.6	48.5	55.0	450.82*
No. years postmenopausal	33.8	23.4	14.37*	36.7	27.4	19.2	85.10*
No. pregnancies	1.6	2.1	3.60**	1.3	1.9	2.7	10.87*
Ever used oral contraceptives, %	5.3	10.9	5.37*	2.9	9.3	10.7	3.57**
Ever used estrogen, %	73.9	69.9	1.04	68.6	64.6	54.7	3.43
Currently use estrogen, %	31.4	33.7	0.32	20.0	25.6	25.3	0.95
Bilateral oophorectomy, %	35.0	25.8	5.35*
Use thiazide, %	8.0	10.0	0.69	8.6	8.1	6.7	0.21
Ever smoked, %	46.9	53.2	2.11	48.6	50.8	54.7	0.57
Wrist BMD, g/cm ²	0.201	0.221	2.50***	0.188	0.208	0.228	3.59**
Radius BMD, g/cm ²	0.559	0.587	2.93***	0.527	0.565	0.591	6.82*
Spine BMD, g/cm ²	0.858	0.894	2.27**	0.811	0.873	0.908	5.24***
Hip BMD, g/cm ²	0.743	0.783	3.18***	0.682	0.771	0.766	11.25*

Note. Comparisons by timing of menopause were performed with *t* tests for continuous variable and chi-square tests for categorical variables. Comparisons by categorical number of reproductive years were performed with analysis of variance for continuous variables and chi-square tests for categorical variables. BMD = bone mineral density.
P* < .001; *P* < .05; ****P* < .01.

at menarche and had been postmenopausal for a significantly longer time. Older women also had had significantly fewer pregnancies and were less obese, as estimated by the body mass index. Fewer older women reported current or ever use of estrogen, past use of oral contraceptives, or cigarette smoking. There were no significant differences by age in the proportion who reported having had a bilateral oophorectomy or in the proportion who had ever used thiazide medications.

Table 2 compares bone mineral density and other measured variables in women who had had early (before age 48) and later menopause and who had had less than 30, 30 to 39, and 40 or more reproductive years. On average, the 226 women in the early menopause group had their last menstrual period at 42 years of age, compared with 52 years for women in the late menopause group (*t* = 30.45, *P* < .001), and a significantly longer time had elapsed since menopause for women in the early menopause group than for women in the late menopause group. Women in the early menopause group did not differ significantly from those in the later menopause group by current age, obesity, age at menarche, cigarette smoking, estrogen use, or thiazide use, but they had had significantly fewer pregnancies, were less likely to have used oral contraceptives, and were more likely to have had a bilateral oophorectomy. Women with an

TABLE 3—Multiply-Adjusted Comparisons of Bone Mineral Density (BMD), by Timing of Menopause and Number of Reproductive Years, Women Aged 60–89 Years, Rancho Bernardo, Calif, 1988 through 1991

	Wrist BMD	Radius BMD	Spine BMD	Hip BMD
Timing of menopause				
Early	0.202	0.562	0.857	0.744
Late	0.220	0.585	0.895	0.783
F	6.05*	7.77*	6.27*	13.38**
No. reproductive years				
<30	0.188	0.532	0.814	0.692
30–39	0.211	0.567	0.874	0.774
≥40	0.223	0.580	0.901	0.749
F	3.13***	5.28*	4.78*	13.40**

Note. Multiply-adjusted comparisons were performed with analysis of covariance. Comparisons were adjusted for age, obesity, estrogen use, past use of oral contraceptives, number of pregnancies, cigarette smoking, and thiazide use. Comparisons by timing of menopause were also adjusted for type of menopause (natural or surgical, i.e., bilateral oophorectomy).
P* < .01; *P* < .001; ****P* < .05.

early menopause had lower bone density at all sites than did women with a later menopause.

Bone mineral density at all sites was significantly positively associated with number of reproductive years (Table 2). No significant differences by number of reproductive years were found in age, obesity, or the proportions of women reporting ever or current use of estrogen, cigarette smoking, or thiazide medication use. Age at menopause, past use of oral contraceptives, and number of pregnancies increased as number of reproductive

years increased, whereas age at menarche and number of years post menopause decreased as number of reproductive years increased.

As shown in Table 3, after adjustment for age, obesity, estrogen use, past oral contraceptive use, number of pregnancies, thiazide use, cigarette smoking, and bilateral oophorectomy, there were significant differences by timing of menopause and by number of reproductive years in bone mineral density of the ultradistal wrist, midshaft radius, lumbar spine, and total hip. For each of these

TABLE 4—Relationship^a of Age at Menopause and Number of Reproductive Years to Bone Mineral Density (BMD), Multiple Regression Analysis, Women Aged 60–89 Years, Rancho Bernardo, Calif, 1988 through 1991

	Wrist BMD			Radius BMD			Spine BMD			Hip BMD		
	β	F	R ²	β	F	R ²	β	F	R ²	β	F	R ²
Age at menopause												
All women (n = 555)												
Covariates	0.12	0.30	0.13	0.29
+Age at menopause	0.002	9.07*	0.14	0.003	20.00**	0.33	0.005	19.13**	0.16	0.004	21.94**	0.32
Natural menopause only (n = 391)												
Covariates	0.17	0.30	0.15	0.30
+Age at menopause	0.002	3.98***	0.17	0.003	10.56**	0.32	0.006	14.05**	0.18	0.003	9.47*	0.32
Oophorectomy only (n = 164)												
Covariates	0.07	0.25	0.08	0.25
+Age at menopause	0.002	4.02***	0.17	0.003	7.30*	0.29	0.004	4.85***	0.11	0.005	11.74**	0.30
Nonsmokers (n = 274)												
Covariates	0.11	0.32	0.09	0.29
+Age at menopause	0.003	14.74**	0.15	0.003	11.60**	0.35	0.004	9.51*	0.12	0.003	11.59**	0.31
Reproductive years (n = 391)												
Covariates	0.16	0.30	0.15	0.30
+No. reproductive years	0.001	3.95***	0.17	0.002	9.38*	0.32	0.006	15.16**	0.18	0.003	9.01*	0.32

^aAfter adjustment for covariates. Covariates were age, obesity, estrogen use, past use of oral contraceptives, number of pregnancies, cigarette smoking, and thiazide use. Analyses of age at menopause and bone density were also adjusted for type of menopause (natural or surgical, i.e., bilateral oophorectomy).

* $P < .01$; ** $P < .001$; *** $P < .05$.

sites, bone mineral density was lowest among those with an early menopause and among those with the fewest reproductive years and increased with increasing number of reproductive years.

When age at menopause was examined as a continuous variable in multiple regression analyses, early menopause (adjusted for age, obesity, cigarette smoking, past oral contraceptive use, number of pregnancies, bilateral oophorectomy, use of estrogen, and use of thiazide medications) remained a significant independent predictor of reduced bone mineral density at all sites (Table 4). Similar results were found when the regression analyses were restricted to women with natural menopause, to women with surgical menopause, and to women who had never smoked cigarettes. In every analysis, there was a significant and positive association between age at menopause and bone mineral density. Number of years post menopause accounted for a similar amount of variability in bone mineral density at each site, as did age at menopause (data not shown). Table 4 also shows the results of regression analyses examining the association of number of reproductive years as a continuous variable with bone mineral density after adjustment for age, obesity, cigarette smoking, past oral contraceptive use, number of pregnancies, and use of estrogen and thiazide medica-

tions. Number of reproductive years had significant positive associations with bone mineral density at all sites.

In separate regression models restricted to women with a natural menopause and adjusted for all variables, the proportions of variance explained by age at menarche were 0.10% for wrist bone mineral density, 0.0025% for radius, 0.35% for spine, and 0.01% for total hip. The corresponding proportions of variance explained by age at menopause were 0.88% for wrist bone mineral density, 2.02% for radius, 3.13% for spine, and 1.77% for total hip. In contrast, the proportions of variance explained by number of reproductive years were 1.00% for wrist bone mineral density, 2.56% for radius, 3.96% for spine, and 2.43% for total hip. At every site, total number of reproductive years explained more of the variance in bone mineral density than did either age at menarche or age at menopause.

Discussion

All women experience slow bone loss with age, accelerated bone loss at menopause, and reduced bone loss with estrogen replacement.¹ In this community-dwelling cohort, elderly women who had an early menopause remained at a disadvantage with regard to bone mineral density at both axial and appendicular sites,

many years after the stage of accelerated perimenopausal bone loss.

In these older, postmenopausal women, the age at menopause and number of reproductive years were significantly and positively associated with bone mineral density at the wrist, radius, spine, and total hip. These associations were not explained by age, obesity, number of pregnancies, estrogen use, past oral contraceptive use, cigarette smoking, or thiazide medication use, and adjustment for these characteristics did not eliminate the associations. Furthermore, the associations of age at menopause with bone mineral density were similar for women with a natural menopause and women with a surgical menopause.

It is extremely difficult to compare different studies of osteopenia, given differences in study design, bone measurements, age, and source of study subjects. Many studies have included a large proportion of perimenopausal women who were probably still in a variable and rapid stage of bone loss, which complicates interpretation. In addition to age at menopause, other factors (such as obesity, cigarette smoking, and use of thiazides and estrogen) determine which women will have clinically significant bone loss. As Nordin et al.¹⁶ pointed out, women reach the menopause with variable amounts of bone; therefore it should not be surprising

that differences due to the menopause wash out over time, particularly in studies involving small numbers of women. For example, Seeman et al.¹⁷ recently reported no significant difference in the bone mass of postmenopausal women who had had an early menopause compared with those who had had menopause at a normal age. Richelson et al.⁴ found that bone density in fourteen 54-year-old prematurely oophorectomized women who had been postmenopausal for 20 years was the same as in fourteen 73-year-old women, also postmenopausal for 20 years, leading to the conclusion that most bone loss was due to estrogen deficiency.

Few studies have examined the remote consequences of early menopause for elderly women. In the study most similar to the present report, Gardsell et al.³ found that among women aged 50 to 69 years, those who reported that menopause occurred before age 46 had significantly lower initial bone mass and, over the next 11 years, a significant excess of "fragility fractures." In contrast to the present study, age at menopause was unrelated to fracture rate in women aged 70 years and older, but follow-up in this age group was incomplete and baseline bone mass was not reported.

The results of the present study are in accord with those of Melton et al.¹² and Vico et al.,¹³ who reported positive associations of reproductive years with bone density of the lumbar spine. In a somewhat similar study, Georgiou et al.¹⁸ reported a positive association between number of menstrual cycles experienced and bone mineral content of the radius in postmenopausal women. Ours is the first study to show an increase with reproductive years in bone mineral density at all four sites examined and to compare this association with other reproductive variables.

As reported by others, age at menarche has negative associations⁵⁻⁹ and age at menopause has positive associations¹⁻⁴ with bone mineral density; each of these studies assessed a woman's standing on only one dimension. In our cohort, categorizing a postmenopausal woman by her number of reproductive years was more predictive of her bone density and risk of osteoporosis than either one of the component variables separately. Although number of reproductive years explained only a small amount of the variance in bone mineral density, this variable was superior to age at menarche alone and slightly better than age at menopause alone.

Several potential sources of bias were considered. Ages at menarche and

menopause were both assessed by self-report. Although Cummings¹⁹ found women's recall of their reproductive history to be quite reliable, we recognize the limitations of self-report; older women may incorrectly recall menarche as occurring later than the menarche reported by younger women. Women in the oldest age groups did report a later menarche than the youngest women. However, similar findings have been reported for other American women^{8,12} and for Japanese women,²⁰ and they very likely reflect secular trends occurring in age at menarche. The average age at menopause did not change, which has also been reported by others.^{21(p4),22(p8)} Furthermore, it is probable that any misclassification of women who did not accurately report age at menarche or menopause would be randomly related to bone density. Random misclassification would reduce the magnitude of associations, thus introducing a conservative bias. By analyzing data from women with surgical and natural menopause separately, we reduced the potential confounding of altered endogenous endocrine states leading to oophorectomy. We cannot exclude the possibility that differences were due in part to those with fewer reproductive years and early age at menopause being temporally closer to menopause; the sample size was not large enough to stratify by number of years post menopause. Finally, cigarette smoking, a major determinant of early menopause,²³ was not an important confounder here—probably because only 17% of the ever smokers had smoked more than a pack of cigarettes per day.

We conclude that classification of women by number of reproductive years (in conjunction with other known risk factors for osteoporosis) may be more helpful than classification by age at menopause alone in identifying women who are at increased risk of osteoporosis. The results of this study offer further evidence for the long-term consequences of estrogen deficiency and suggest that estrogen replacement should be considered to prevent osteoporotic fractures in women with early surgical or nonsurgical menopause or women with relatively few reproductive years, whether or not their bone density is within the normal range at the time of menopause. □

Acknowledgments

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Conference on Behavioral Symptoms in Dementia to Be Held in Cleveland

A symposium on "Behavioral Symptoms in Dementia: Theories and Therapies" will be held in Cleveland, Ohio, September 30-October 1, 1993. This conference is designed to address the phenomenology of behavioral symptoms of Alzheimer's Disease, the conceptual frameworks of the symptoms' biology and psychology, and the biological and behavioral interventions that enhance their management.

The program will feature nationally known specialists and is sponsored by the NIA Alzheimer's Disease Center of Uni-

versity Hospitals of Cleveland and Case Western Reserve University; the Cleveland Chapter of the Alzheimer's Association; the National Alzheimer's Association; the Western Reserve Geriatric Education Center; and the CWRU Center on Aging and Health. Continuing education credits are available.

For further information contact the Conference Secretary, Alzheimer Center, University Hospitals of Cleveland, 2074 Abington Rd, Cleveland, OH 44106; tel (216) 844-7360.