Published in final edited form as:

Menopause. 2015 October ; 22(10): 1035–1044. doi:10.1097/GME.0000000000000451.

Effect of Age of Self-Reported, Non-Surgical Menopause on Time to First Fracture and Bone Mineral Density in the Women's Health Initiative Observational Study

Shannon D. Sullivan, MD, PhD¹ [Staff Physician], Amy Lehman, MAS², Fridtjof Thomas, PhD³, Karen C. Johnson, MD, MPH³, Rebecca Jackson, MD⁴, Jean Wactawski-Wende, PhD⁵, Marcia Ko, MD⁶, Zhao Chen, PhD, MPH⁷, J David Curb, MD, MPH^{8, #}, and Barbara V. Howard, PhD⁹

¹Medstar Washington Hospital Center, Department of Medicine, Division of Endocrinology & Metabolism, 110 Irving St, NW, Suite 2A-72, Washington, DC 20010, 202-877-6563 (phone), 202-877-6588 (fax), Shannon.d.sullivan@medstar.net

²Center for Biostatistics, The Ohio State University. Columbus, OH

³Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN

⁴Department of Medicine, The Ohio State University, Columbus, OH

⁵Department of Social and Preventive Medicine, State University of New York, University at Buffalo, Buffalo, NY

⁶Department of Women's Health Internal Medicine, Mayo Clinic, Phoenix, AZ

⁷Department of Epidemiology & Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

⁸Department of Geriatric Medicine, University of Hawaii, Honolulu, HI

⁹Department of Medicine, Biostatistics & Epidemiology, Medstar Health Research Institute, Hyattsville, MD

Abstract

Objective—Menopause is a risk factor for fracture, thus menopause age may affect bone mass and fracture rates. We compared Bone Mineral Density (BMD) and fracture rates among healthy postmenopausal women with varying ages of self-reported non-surgical menopause.

Methods—Hazard ratios for fracture and differences in BMD among 21,711 postmenopausal women from the Women's Health Initiative Observational cohort without prior hysterectomy, oophorectomy, or hormone therapy, who reported age of menopause of <40, 40–49, or ≥50 years, were compared.

Correspondence to: Shannon D. Sullivan.

#(Author deceased)

Disclosures: No author has a conflict of interest or financial disclosure that is relevant to the subject matter or materials included in this work.

Results—Prior to multivariable adjustments, we found no differences in absolute fracture risk among menopausal age groups. After multivariable adjustments for known risk factors for fracture, women undergoing menopause <40 had a higher fracture risk at any site compared to women undergoing menopause ≥50 years (HR=1.21, 95% CI: 1.02, 1.44; p=0.03). In a subset with BMD measurements (n=1,351), whole body BMD was lower in women who reported menopause <40 compared to 40–49 years (estimated difference= −0.034 g/cm²; 95% CI: −0.07, −0.004; p=0.03) and compared to ≥50 years (estimated difference= −0.05 g/cm²; 95% CI: −0.08, −0.02; p<0.01). Left hip BMD was lower in women with menopause <40 compared to ≥50 years (estimated difference= −0.05 g/cm²; 95% CI: −0.08, −0.01; p=0.01), and total spine BMD was lower in women with menopause <40 compared to ≥50 and 40–49 years (estimated differences= −0.11 g/cm²; 95% CI: −0.16, −0.06; p<0.01 and −0.09 g/cm²; 95% CI: −0.15, −0.04; p<0.01, respectively).

Conclusions—In the absence of hormone therapy, earlier menopause age may be a risk factor contributing to decreased BMD and increased fracture risk in healthy postmenopausal women. Our data suggest that menopause age should be taken into consideration, along with other osteoporotic risk factors, when estimating fracture risk in postmenopausal women.

Keywords

fracture; menopause; premature menopause; bone mineral density

INTRODUCTION

Fractures are a significant cause of morbidity and mortality among aging individuals. Mortality rates are reported to be as high as 30% within the first year following a fracture of the spine or hip^{1,2}, and increased morbidity is largely related to diminished quality of life caused by fracture-induced disability³. Multiple risk factors for decreased bone mass, and thus for predisposition for fractures, have been identified, including (among others) female sex, advancing age, low body weight, Caucasian race, nulliparity, alcohol and tobacco use, vitamin D deficiency, and low dietary calcium intake⁴. Menopause is associated with increased risk for fracture in women, with multiple factors playing a role, including advancing age, loss of the anti-resorptive effect of estrogen on bone, changes in body composition, changes in activity level, ethnicity, and parity^{5,6}. Further, in women who experience menopause at very young ages, optimal bone accrual may not have occurred, which may also contribute to increased fracture risk later in life. Indeed, minimizing fracture risk is an important aspect of the long-term clinical care of postmenopausal women.

The average age of menopause is approximately 52 years; however, many women experience menopause at slightly younger ages. Women who enter menopause earlier may be at greater risk than expected for their chronological age for fractures due to a longer duration of post-menopausal bone loss and in some cases, reduced bone accrual. It is well-established that young (pre-menopausal) women with syndromic forms of premature ovarian failure (defined clinically as ovarian failure or insufficiency prior to age 40) have low age-related BMD^{7–12}. On the other hand, many other factors also play a role in determining ultimate BMD and fracture risk in post-menopausal women, thus menopause age may have less overall impact in older age. Whether or not, and to what extent, otherwise healthy

postmenopausal women without syndromic forms of premature menopause, but who experience menopause earlier than the average age, have differences in bone mass or fracture risk due to menopause age has not been previously investigated.

The Women's Health Initiative Observational Study (WHI OS) is a large prospective cohort study designed to investigate risks for chronic disease, including risk for fractures, in relatively healthy postmenopausal women. Two of the study's primary outcome measures were occurrence of fractures, and in a small subset, absolute BMD and change in BMD over time. Here, we analyzed WHI OS data to determine if age of menopause among women in the WHI OS cohort is associated with fracture occurrence and/or BMD.

METHODS

93,676 postmenopausal women were recruited between October 1, 1993, and December 31, 1998, at 40 WHI study sites in the United States. Detailed descriptions of the WHI eligibility criteria, study design and methods have been previously published¹³. Briefly, women aged 50–79, without medical co-morbidities that precluded survival for at least three years following study entry, were eligible to participate. Each study participant provided written informed consent through the approving Institutional Review Board (IRB) at her respective study site. Local IRBs at each study site, the NIH, and the Coordinating Center IRB approved the protocols.

At study enrollment, the following information was collected from all participants using standardized questionnaires: demographic information; complete personal medical history, including medication history and current medication use, smoking status, alcohol consumption, and recreational physical activity level; and family history. Participants were instructed to bring all of their medications, including over-the-counter and supplement medications, to the clinic for verification of use. Current or prior use of hormone therapy (HT) was carefully documented. Information was also collected on baseline risk for fractures (such as family history or personal history of fractures) using standardized questionnaires. This included assessment of total daily calcium intake from both dietary sources and supplements. Updated information was collected annually through mailed follow-up questionnaires. A physical examination was performed at study entry to assess height, weight, and blood pressure, and then again after 3 years.

For all participants in the WHI, fracture occurrences were recorded yearly. Fractures were categorized by site: hip/pelvis/upper leg, lower leg/ankle/knee, foot, upper arm/shoulder/elbow, lower arm/wrist/hand, and spine/tailbone. For every participant, the first occurrence of a hip fracture was adjudicated and confirmed by WHI physicians; the first occurrences of all other fracture types were based on self-report and were not adjudicated. A small subgroup of WHI OS women underwent dual x-ray absorptiometry (DXA) scan of the lumbar spine (total spine), total hip, and whole body at the time of study entry, and again at the 3-year, 6-year, and 9-year study visits. Among those women undergoing DXA, mean duration of follow up was 7 years. Three of the forty WHI study sites performed DXA scans (Pittsburgh, PA; Birmingham, AL; Tuscon, AZ) (QDR2000, 2000+, or 4500W; Hologic Inc., Bedford, MA), with low inter-scan variability among the three sites (<1.5% for spine,

4.8% hip, and 1.7% for linearity) based on weekly phantom scans performed as a quality control measure.

In this secondary analysis of the WHI OS, we investigated the impact of self-reported age of non-surgical menopause on cumulative fracture occurrence and change in BMD over time. Menopause age was defined as a woman's age at the time of her final menstrual period; this definition helps to avoid confounding our analyses with data from women with oligo- or amenorrhea due to other causes. Of the original 93,676 women in the WHI OS, we excluded 3,951 women who were missing information on menopausal status at screening. To further avoid confounding our data with women who were exposed to estrogen following reported age of menopause (due to either surgical menopause or HT use), we also excluded 68,014 OS women with (i) total abdominal hysterectomy (TAH) and/or bilateral oophorectomy (BSO) (unless performed at an older age than the reported age of menopause), (ii) self-reported history of HT at baseline, or (iii) self-reported use of HT during the study. Of the original 93,676 women in the WHI OS, a total of 21,711 women met all of our inclusion criteria (i.e., not missing menopause information, no TAH and/or BSO, no history of HT use at baseline or reported use of HT during the study) and were included for this analysis. These women were then divided into 3 groups based on reported age of non-surgical menopause: i) menopause prior to age 40 (<40), ii) menopause between ages 40 and 49 (40–49), and iii) menopause at age 50 or later (≥ 50). These age categories were pre-specified in the WHI OS. Clinically speaking, these age categories also divide women between those who underwent menopause at the population mean age (≥ 50) and those who experienced menopause at earlier ages. A small subset of the eligible 21,711 women in our study (n=1,351; 6.2%) had at least one DXA scan during the course of the study. This is similar to the percentage of women in the entire WHI OS cohort with BMD data (6,482 of 93,676 women; 6.9%), thus the subgroup of women in our sub-study with available BMD data adequately represents our study population as compared to the entire WHI OS cohort. DXA results were used to compare changes in BMD over the study period between the three menopause age groups.

Because over 70% of all women in the WHI OS who reported age of menopause before age 40 also reported past or current HT use, we also compared demographics and risk factors for osteoporosis between uterus-intact women with the earliest ages of self-reported menopause (< age 40 years) reporting current or past use of HT (who were excluded from our primary analysis), and uterus-intact women with menopause <40 with no current or past HT use (our primary cohort), to determine if baseline risk factors in the non-HT group may have contributed to any differences we found.

Statistical analyses

Baseline demographics were summarized by age of menopause (<40, 40–49, and ≥ 50). Baseline demographics were also summarized for women with menopause age <40 by presence or absence of any HT use. For continuous variables, the mean, standard deviation, and range were calculated. For categorical variables, the frequency and percentages are reported.

Our primary aim was to compare the risk of first fracture at the hip (adjudicated) and at any site (non-adjudicated) between the three specified menopause age groups. We considered

time from enrollment (days) to first adjudicated hip fracture, as well as time from enrollment (days) to any fracture (i.e., adjudicated and non-adjudicated fractures), as separate primary outcomes. For all fracture types, we have records only of the first occurrence of each type; therefore, we present analyses on time to first fracture during the observation period. Cumulative hazard plots using time (days) to first fracture were generated, and Cox models were applied to the data to assess the impact of menopause age on the risk of fracture. Multivariable models were adjusted for the following patient factors: age at enrollment, body weight, ethnicity, smoking status, alcohol consumption, intake of calcium and vitamin D, history of bisphosphonate or glucocorticoid use, history of diabetes, total energy expenditure from recreational physical activity (MET-hours/week), self-reported number of falls in the previous 12 months, and personal history of any fracture at the time of screening, all of which are associated with fracture risk in postmenopausal women. Summaries of these variables by menopause age are shown in Table 1. Due to the small numbers of women with available BMD data, we were unable to adjust for BMD in our multivariable model; therefore, we cannot conclude that any differences we found in fracture risk among the menopause groups are independent of differences in BMD. For all models, there were no significant two-way interactions with any of the covariates and menopause age. Scaled Schoenfeld residuals were examined; for models involving time to first self-reported fracture, the interaction between time (natural log scale) and age at enrollment was included due to concerns about non-proportionality. Estimated hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

To correct for a disparity in sample sizes among the 3 menopause groups (<40, n=524; 40–49, n=6,626; 50, n=14,561), we repeated our multivariable analyses using propensity score methods to match the numbers of women with menopause <40 to the numbers of women with menopause 40–49 and 50. We developed a propensity score based on a multinomial logistic model using all of the demographic factors in Table 1. We then matched the 524 women with menopause <40 with 524 women with menopause 40–49 and 524 women with menopause 50 separately using nearest-neighbor matching without replacement and a conservative caliper of 0.01. The HR and 95% CI from the Cox models using the matched sample were calculated, using robust standard errors, and overall conclusions from the matched set are consistent with our multivariable adjusted models (*data not shown*).

Our secondary aim was to determine the association between menopause age and BMD as measured by DXA. A small subset of our original study population had at least one BMD measurement (n=1,351 subjects with whole body and/or left hip + total spine DXA). The number of BMD measurements varied by individual; in the final multivariable models, the maximum number of measurements per individual was 4. Linear mixed effects models were used to assess changes in whole body, left hip, and total spine BMD as age increased for each individual, adjusting for age at enrollment, body weight, ethnicity, smoking status, alcohol consumption, intake of calcium and vitamin D, history of bisphosphonate or glucocorticoid use, history of diabetes, total energy expenditure from recreational physical activity (MET-hours/week), self-reported number of falls in the previous 12 months, and personal history of any fracture at the time of screening. Age at BMD measurement was centered by subtracting the age at BMD measurement from 50 years; the intercept term in

the model using these centered values therefore estimated BMD at age 50 (the minimum age at enrollment into WHI OS). Linear mixed effects models were then fit to the data, using the centered age at BMD measurement as the time variable. The model allowed for each individual to have a separate intercept and change over time (slope) based on her available data; from these individual intercepts and slopes, an overall (mean) intercept and slope for each menopause age group was calculated. In sum, we fit linear models for each menopause age group to estimate BMD over time, using age as the primary predictor of BMD. Figure 2 thus represents the changes in BMD over time (the slope of each line) for each menopause age group, as estimated from these models. From these linear mixed effects models, we then compared mean estimated BMD differences between the three menopause groups.

P-values ≤ 0.05 were considered significant. All analyses were performed using SAS/STAT software, Version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata/SE 10.1 (StataCorp 2007, *Stata*).

RESULTS

Of the 89,725 WHI OS participants who had menopause information, 68,014 women with histories of TAH, BSO, or prior or current HT use were excluded, leaving 21,711 women for our primary analysis. Among the 21,711 women, there were a total of 5,769 self-reported fractures during follow-up, including 593 adjudicated hip fractures. Baseline demographic characteristics of these women, grouped by menopause age, are shown in Table 1. The demographic differences between menopause age groups shown here guided our multivariable adjustments for both primary and secondary analyses.

Comparison of demographics and osteoporotic risk factors between uterus-intact women with menopause <40 who reported never using HT ($n=685$) and uterus-intact women with menopause <40 who had ever used HT (and who were thus excluded from our primary analysis, $n=1,899$), are shown in Table 2. We saw several differences in demographics and osteoporotic risk factors between these groups, including age at screening, race, smoking status, alcohol use, activity level, rates of obesity, calcium and vitamin D intake, and diabetes status. There were no differences between the two groups in number of years since menopause at screening, number of reported falls in the 12 months prior to screening, and use of glucocorticoids or bisphosphonates.

Overall, we found no significant differences in the percentage of women in each menopause group with ≥ 1 hip ($p=0.59$) or ≥ 1 hip plus all other self-reported fractures ($p=0.63$) during the OS study period. From our primary cohort of women, cumulative hazard plots for adjudicated hip fractures (Figure 1a) and all fractures (self-report + hip, Figure 1b) were created using time (days) from study entry until first fracture after adjusting for age at screening. Age at screening was in fact the most significant predictor of both adjudicated hip as well as any self-reported fracture for all models ($p < 0.001$), with older women having a higher fracture risk. In simple models with age as the only covariate, there were no significant differences between menopause age groups for either adjudicated hip fracture or any self-reported fracture (Table 3). However, after adjusting for other covariates and applying our multivariable model, we found that the rate of any fracture for women who

reported menopause prior to age 40 was greater than the fracture rate among women with menopause age 50 (HR = 1.21, 95% CI: 1.02, 1.44; $p = 0.03$, Table 3). Due to the small numbers of women with available BMD data, we were unable to determine if these differences in fracture risk were independent of differences in BMD using this model.

In the small subset of women in whom BMD assessments were performed, the majority of participants had 2–3 BMD measurements (range: 1–5). Separate linear mixed effects models were used to estimate changes in whole body, left hip, and total spine BMD over time, using age as the primary predictor along with all previously listed variables as covariates; estimated slopes from these models by menopause group are shown in Figure 2. There were no statistically significant interactions between age at the time of initial DXA scan and menopause group ($p=0.87$, $p=0.24$, and $p=0.94$ for whole body, left hip, and total spine BMD, respectively), suggesting differences in BMD between menopause groups were consistent across age (Figure 2). Left hip BMD estimates in all menopause groups decreased with increasing chronological age ($p<0.01$), whereas whole body BMD estimates did not change significantly with increasing chronological age ($p=0.08$) and total spine BMD estimates increased with increasing age at the time of DXA scan ($p<0.01$) (Figure 2).

From these models, we calculated differences in estimated BMD at the whole body, left hip, and total spine between the 3 menopause age groups (Table 4). There were statistically significant decreases in estimated BMD at the left hip, total spine, and whole body as age of menopause decreased, with the exceptions of no difference in estimated left hip BMD between women with menopause <40 *versus* 40–49 years and no difference in estimated total spine BMD between women with menopause 40–49 *versus* 50 years (Table 4). Overall, we found significant decreases in BMD or trends toward decreasing BMD with younger menopause ages.

The total number of hip fractures and total fractures occurring within each menopause group, in *a*) our larger primary cohort of women and in *b*) our subgroup of women with DXA data, is presented in Table 5 for comparison. Of note, there were no significant differences in the prevalence of hip or total fractures among the three menopause age groups in our larger primary cohort ($p=0.59$ for hip and $p=0.63$ for total fractures, Table 5a), nor were there differences in the prevalence of hip or total fractures among the three menopause groups in our subgroup of women for whom DXA data were collected ($p=0.67$ for hip and $p=0.24$ for total fractures, Table 5b), despite our finding of declines in BMD with decreasing menopause age.

DISCUSSION

This analysis of a large longitudinal cohort of women with standardized outcomes data evaluates, for the first time, the effect of age of self-reported, non-surgical menopause on fracture risk and BMD. In this secondary investigation of the WHI OS, we demonstrate that among postmenopausal women who have undergone non-surgical menopause and have never taken HT, younger age of self-reported menopause may have a negative impact on BMD and fracture risk. Absolute fracture rates did not differ based on menopause age; however, in our multivariable model, we found an increased HR for fracture among women

with menopause prior to age 40 compared to women with menopause at age 50 or later. Then, using a linear mixed effect model to estimate changes in BMD over time at the left hip, total spine and whole body, we also found that women with younger ages of menopause had lower BMD at all sites. Overall, these data suggest that younger age of self-reported menopause negatively impacts BMD and overall fracture risk during the menopausal years, and therefore, that age of menopause in women never receiving HT should contribute to clinical assessments of post-menopausal fracture risk.

Cumulative hazard plots for time (days) from study entry to first fracture were calculated in uterus-intact women without current or prior HT use because this period was considered known 'exposure' time to factors that contribute to postmenopausal bone loss, including advancing age, decreased activity levels, decreased body weight, and a decline in ovarian hormone production. We believe that removing HT as a confounding variable, rather than attempting to control for use of HT in a model, was justified, thus we excluded women in all three menopause age groups who reported any past or current HT use. Of note, the average age at screening in the WHI OS was approximately 64 years; therefore, women who experienced menopause before age 40 had a considerably longer time between reported age of menopause and enrollment, when monitoring for fractures began (average time: 29 years) compared to women with menopause between ages 40 and 49 (average time: 18 years) or to women with menopause at age 50 and older (average time: 11 years). Despite these differences in 'exposure time,' we found no differences in absolute fracture risk based on menopause age. After multivariable adjustments, however, we found small decreases in BMD and increases in fracture risk among women who reported menopause < 40 compared to women with older menopause ages. These data thus suggest that menopause age is one clinically significant independent risk factor for fracture in the post-menopausal years, and that menopause age, together with other risk factors, influences postmenopausal fracture risk in otherwise healthy women.

Although our multivariable analyses demonstrated an increase in risk for any fracture among women with menopause <40 years compared to the older menopause age groups, these data may be confounded by the small numbers of women with reported age of menopause <40 and no HT use among the WHI OS cohort (n=524). Furthermore, we found that women with menopause <40 who were *not* treated with HT (our cohort) tended to have more osteoporotic risk factors compared to women with menopause <40 who did receive HT (and who were thus excluded from our primary analysis). It is possible that these differences contributed, at least in part, to the increase in fracture risk we saw in women with early menopause who were never treated with HT. That said, our data are consistent with data in women with syndromic forms of premature ovarian failure, such as Turner's Syndrome (TS) and 46XX primary ovarian insufficiency (POI), who are at risk for decreased BMD for age that is due, at least in part, to exposure to menopausal levels of estrogen at young ages⁹⁻¹². It remains to be investigated whether hormone therapy with physiologic doses of estrogen in women with non-syndromic early age of menopause will help to maintain BMD and/or reduce fracture risk, as it has been shown to do in women with POI and TS^{9,10,14}.

Interestingly, mean BMI in all menopause age groups was between 25 and 30 mg/kg² (overweight) (Table 1). Being either underweight or obese is associated with loss of

BMD^{15,16}. Given that women in this study were overweight (as opposed to underweight or obese) as a group and that mean BMI was clinically similar among the three menopause age groups suggests that BMI differences were not responsible for the differences in BMD and fracture risk demonstrated here.

We found a higher prevalence of African American (AA) and Hispanic women compared to Caucasian women among participants reporting menopause before age 40. Given that Caucasian race itself is a risk factor for osteoporosis and fractures, the increased prevalence of AA and Hispanic women with menopause <40 would be expected to contribute to increased BMD and decreased fracture risk in this group. However, we demonstrated no differences in absolute fracture risk, and after multivariable adjustments, *decreases* in BMD and slightly *increased* HR for fracture in women with earlier menopause. Together, these data are consistent with multiple risk factors acting together to determine ultimate fracture risk, and suggest that no single risk factor may be able to independently predict post-menopausal loss of bone mass or fracture risk. That being said, advancing chronological age was the strongest predictor of fracture risk in our cohort, and a significantly greater contributor compared to self-reported menopause age.

Strengths of this study include a large cohort of healthy postmenopausal women, careful follow-up, and detailed data collection on multiple covariates impacting bone density and fracture risk, such as physical activity, alcohol and tobacco use, and use of medications such as glucocorticoids and bisphosphonates. Furthermore, the availability of comparable DXA measurements from a subset of these women over time allowed us to compare BMD among the menopause groups.

Study limitations include a lack of information on use of medications that may have affected BMD *prior* to study entry, with the exception of prior use of HT. Second, menopause age was recorded based on participant self-report and was not confirmed with hormonal testing (ie, menopausal range FSH and/or estradiol levels), thus it is possible that some women reported menopause due to prolonged amenorrhea, but were not yet truly menopausal, or that menopause age was reported later than it actually occurred. Menopause age was defined as the age of the final menstrual period, thus to the extent that menopause age was reported erroneously early or late by study participants, we expect that each of our menopause age groups were affected similarly. Third, we collected data on calcium and vitamin D intake through supplements and the diet; however, we did not measure serum 25-hydroxy-vitamin D levels among WHI OS participants, thus vitamin D deficiency could not be accounted for as a potential contributor to fracture risk. Additionally, we only have adjudicated data on fractures that occurred *after* study enrollment, thus any fractures occurring prior to study entry were not included in our hazard functions. We do not believe, however, that exclusion of prior fractures has significantly impacted our results, because at enrollment, only 158 out of the 21,711 women included in this analysis reported an osteoporosis-related fracture prior to enrollment [7 (1.3%) in the menopause <40 group; 43 (0.7%) in the menopause 40–49 group; and 108 (0.7%) in the menopause ≥ 50 group]. Finally, study power was limited by the number of WHI OS participants without prior TAH/BSO and/or HT use who also had BMD data. The small numbers of women with both fracture occurrence and DXA data in our analysis prevented us from reliably including BMD as a co-variate in our multivariable

analyses for fracture risk, thus we cannot be certain that differences in the HRs for fracture among the menopause age groups were independent of differences in baseline BMD. That said, we demonstrated decreases in BMD among women with younger menopause ages, suggesting that the increase in fracture rates we saw in women with earlier menopause ages may be due, at least in part, to decreased BMD.

CONCLUSIONS

In a large cohort of uterus-intact, healthy postmenopausal women who had never used HT, age of menopause did not alter absolute fracture risk. In multivariable models, however, fracture risk was higher and BMD was lower among women with earlier ages of menopause. These data suggest that in the absence of HT, age of menopause contributes to fracture risk in postmenopausal women, particularly when other osteoporotic risk factors are considered.

Acknowledgments

Funding: The WHI program is funded by the National Heart, Lung and Blood Institute, and the United States Department of Health and Human Services.

Financial support: No additional financial support was obtained for preparation of this manuscript.

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Figure 1. Adjusted cumulative hazard functions

1a. Adjudicated hip fractures

1b. Any fracture + adjudicated hip (based on Cox model with age at screening as covariate, age centered at median of 64)

— Menopause 50 or older - - - Menopause 40-49 . . . Menopause <40

Figure 2. Change over time in estimated whole body (*upper panel*), left hip (*middle*), and total spine (*lower*) BMD (g/cm^2) for each menopause group, calculated from mixed linear effects models.

Table 1

Baseline demographic and clinical characteristics of OS women with no hysterectomy or bilateral oophorectomy prior to menopause and no history of HT use or self-reported HT use during the study by menopause age (n=21,711)

	< 40 (n=524)	40 – 49 (n=6,626)	> 50 (n=14,561)	p
Age group at screening, years	<i>n</i> (%N)	<i>n</i> (%N)	<i>n</i> (%N)	<.01
50 – 59	124 (24%)	1,700 (26%)	3,098 (21%)	
60 – 69	244 (43%)	2,944 (44%)	6,811 (47%)	
70 – 79+	176 (34%)	1,982 (30%)	4,652 (32%)	
Mean (SD) (min, max)	65.4 (7.5) (50 – 79)	64.9 (7.5) (50 – 79)	65.6 (6.9) (50 – 80)	
Years since menopause				<.01
< 10	0 (0%)	994 (15%)	4,906 (34%)	
10 – 19	62 (12%)	2,284 (34%)	6,838 (47%)	
> 19	462 (88%)	3,348 (51%)	2,817 (19%)	
Ethnicity				<.01
White (not of Hispanic origin)	346 (66%)	5,355 (81%)	12,288 (84%)	
Black/African-American	131 (25%)	673 (10%)	1,156 (8%)	
Hispanic/Latino	31 (6%)	282 (4%)	455 (3%)	
American Indian/Alaskan Native	2 (<1%)	27 (<1%)	44 (<1%)	
Asian/Pacific Islander	6 (1%)	175 (3%)	402 (3%)	
Other	8 (2%)	86 (1%)	177 (1%)	
Missing	0 (0%)	28 (<1%)	39 (<1%)	
Weight (kg)				
Mean (sd) (min, max)	74.8 (18.5) (41 – 172)	73.0 (17.8) (36 – 175)	72.5 (17.5) (33 – 195)	<.01
missing	1 (<1%)	41 (1%)	78 (1%)	
Body Mass Index (BMI), kg/m²				
<25	158 (30%)	2,348 (35%)	5,427 (37%)	<.01
25 – <30	166 (32%)	2,249 (34%)	4,938 (34%)	
30	196 (37%)	1,943 (29%)	4,014 (28%)	
Missing	4 (1%)	86 (1%)	182 (1%)	
Mean (sd) (min, max)	28.9 (6.5) (17.1 – 58.3)	28.0 (6.3) (11.9 – 65.3)	27.7 (6.1) (12.0 – 69.2)	
Physical Activity (METS/week)				
0 – 3	196 (37%)	1,880 (28%)	3,594 (25%)	<.01
>3 to <11.75	157 (30%)	2,094 (32%)	4,665 (32%)	
11.75	171 (33%)	2,652 (40%)	6,302 (43%)	
# of falls in the previous 12 months				<.01
0	346 (68%)	4,584 (69%)	9,943 (68%)	
1	101 (19%)	1,255 (19%)	2,875 (20%)	
2	40 (8%)	503 (8%)	1,126 (8%)	

	< 40 (n=524)	40 – 49 (n=6,626)	> 50 (n=14,561)	<i>p</i>
3	24 (5%)	255 (4%)	563 (4%)	<.01
Missing	3 (1%)	29 (<1%)	54 (<1%)	
Smoking status				
Never	245 (47%)	3,288 (50%)	7,865 (54%)	
Past	215 (41%)	2,683 (40%)	5,696 (39%)	<.01
Current	55 (11%)	568 (9%)	833 (6%)	
Missing	9 (2%)	87 (1%)	167 (1%)	
Alcohol consumption				
None	105 (20%)	846 (13%)	1,762 (12%)	<.01
Past use	132 (25%)	1,371 (21%)	2,610 (18%)	
<1 drink/month	68 (13%)	769 (12%)	1,789 (12%)	
<1 drink/week	77 (15%)	1,329 (20%)	2,849 (20%)	
1 to <7 drinks/week	91 (17%)	1,523 (23%)	3,609 (25%)	<.01
7 drinks/week	50 (10%)	743 (11%)	1,854 (13%)	
Missing	1 (<1%)	45 (1%)	88 (1%)	
Diabetes (DM) ever at screening				
No	457 (87%)	6,206 (94%)	13,639 (94%)	<.01
Yes	67 (13%)	414 (6%)	906 (6%)	
Missing	0 (0%)	6 (<1%)	16 (<1%)	
Currently have DM at screening				
No	465 (89%)	6,270 (95%)	13,824 (95%)	<.01
Yes	58 (11%)	344 (5%)	708 (5%)	
Missing	1 (<1%)	12 (<1%)	29 (<1%)	
Oral daily glucocorticoid at screening				
No	516 (98%)	6,541 (99%)	14,403 (99%)	<.01
Yes	8 (2%)	85 (1%)	158 (1%)	
Bisphosphonate use at screening				
No	508 (97%)	6,403 (97%)	14,125 (97%)	
Yes	16 (3%)	223 (3%)	436 (3%)	0.02
Vitamin D intake (mean IU/day)				<.01
< 200	262 (50%)	2,769 (42%)	5,447 (37%)	
200 – <400	86 (16%)	1,125 (17%)	2,692 (18%)	
400 – <600	113 (22%)	1,545 (23%)	3,529 (24%)	
600	63 (12%)	1,187 (18%)	2,903 (20%)	<.01
Calcium intake (mean mg/day)				
<800	272 (52%)	2,606 (39%)	5,107 (35%)	
800 – <1200	109 (21%)	1,518 (23%)	3,539 (24%)	
1200	143 (27%)	2,502 (38%)	5,915 (41%)	

Table 2

Baseline demographic and clinical characteristics of uterus-intact OS women with early menopause (<40 yrs), with or without prior or current HT use

	Early menopause, no HT (n=524)	Early menopause, HT (n=2,017)	p-value
Age group at screening, years			0.01
50 – 59	124 (24%)	528 (26%)	
60 – 69	224 (43%)	953 (47%)	
70 – 79+	176 (34%)	536 (27%)	
Mean (SD) (min, max)	65.4 (7.5) (50 – 79)	64.4 (7.3) (50 – 79)	
Time since menopause, years			0.84
10 – 19	62 (12%)	245 (12%)	
> 19	462 (88%)	1772 (88%)	
Ethnicity			<.01
White (not of Hispanic origin)	346 (66%)	1636 (81%)	
Black/African-American	131 (25%)	211 (10%)	
Hispanic/Latino	31 (6%)	87 (4%)	
American Indian/Alaskan Native	2 (<1%)	15 (1%)	
Asian/Pacific Islander	6 (1%)	40 (2%)	
Other	8 (2%)	20 (1%)	
Missing	0 (<1%)	8 (<1%)	
Body Mass Index (BMI), kg/m ²			<.01
<25	158 (30%)	742 (37%)	
25 – <30	166 (32%)	704 (35%)	
30	196 (37%)	549 (27%)	
Missing	4 (1%)	22 (1%)	
Mean (SD) (min, max)	28.9 (6.5) (17.1 – 58.3)	27.6 (5.6) (15.3 – 65.5)	
Physical Activity (METS/week)			<.01
0 – 3	196 (37%)	574 (28%)	
>3 to <11.75	156 (30%)	630 (31%)	
11.75	171 (33%)	789 (39%)	
Missing	1 (<1%)	24 (1%)	
# of falls in the previous 12 months			0.46
0	356 (68%)	1314 (65%)	
1	101 (19%)	380 (19%)	
2	40 (8%)	171 (8%)	
3	24 (5%)	124 (6%)	
Missing	3 (1%)	28 (1%)	
Smoking status			0.03
Never	245 (47%)	984 (49%)	
Past	215 (41%)	863 (43%)	

	Early menopause, no HT (n=524)	Early menopause, HT (n=2,017)	p- value
<i>Current</i>	55 (10%)	142 (7%)	<.01
<i>Missing</i>	9 (2%)	28 (1%)	
ETOH use			
<i>None</i>	105 (20%)	248 (12%)	
<i>Past use</i>	132 (25%)	458 (23%)	
<i><1 drink/month</i>	68 (13%)	240 (12%)	
<i><1 drink/week</i>	77 (15%)	418 (21%)	
<i>1 to <7 drinks/week</i>	91 (17%)	419 (21%)	
<i>7 drinks/week</i>	50 (10%)	216 (11%)	
<i>Missing</i>	1 (<1%)	18 (1%)	
Diabetes ever at screening			<.01
<i>No</i>	457 (87%)	1870 (93%)	
<i>Yes</i>	67 (13%)	142 (7%)	
<i>Missing</i>	0 (<1%)	5 (<1%)	
Currently have diabetes at screening			<.01
<i>No</i>	465 (89%)	1900 (94%)	
<i>Yes</i>	58 (11%)	109 (5%)	
<i>Missing</i>	1 (<1%)	8 (<1%)	
Glucocorticosteroid taken orally and daily at screening			0.63
<i>No</i>	516 (98%)	1980 (98%)	
<i>Yes</i>	8 (2%)	37 (2%)	
Bisphosphonate use at screening			0.69
<i>No</i>	508 (97%)	1962 (97%)	
<i>Yes</i>	16 (3%)	55 (3%)	
Vitamin D intake (mean IU/day)			<.01
<i>< 200</i>	262 (50%)	717 (36%)	
<i>200 – <400</i>	86 (16%)	324 (16%)	
<i>400 – <600</i>	113 (22%)	527 (26%)	
<i>600</i>	63 (12%)	449 (22%)	
Calcium intake (mean mg/day)			<.01
<i><800</i>	272 (52%)	696 (35%)	
<i>800 – <1200</i>	109 (21%)	464 (23%)	
<i>1200</i>	143 (27%)	857 (42%)	

Table 3

Hazard ratios for hip or any fracture among OS women with no hysterectomy, no history of HT use and no self-reported HT use during follow-up (n=21,711).

Model Type	Outcome	Menopause Comparison	Estimated HR (95% CI)	p-value
Adjusted for age group at enrollment only [†]	Hip fx	< 40 vs. 40 – 49	1.15 (0.69, 1.93)	0.59
		< 40 vs. 50+	1.39 (0.85, 2.25)	0.19
		40 – 49 vs. 50+	1.18 (1.00, 1.41)	0.06
	Any fx	< 40 vs. 40 – 49	1.08 (0.91, 1.29)	0.36
		< 40 vs. 50+	1.12 (0.95, 1.32)	0.18
		40 – 49 vs. 50+	1.04 (0.98, 1.10)	0.23
Multivariable [*]	Hip fx	< 40 vs. 40 – 49	1.13 (0.68, 1.89)	0.62
		< 40 vs. 50+	2.33 (0.80, 2.19)	0.27
		40 – 49 vs. 50+	1.17 (0.98, 1.40)	0.08
	Any fx [†]	< 40 vs. 40 – 49	1.16 (0.98, 1.39)	0.09
		< 40 vs. 50+	1.21 (1.02, 1.44)	0.03
		40 – 49 vs. 50+	1.04 (0.98, 1.10)	0.20

* Multivariable models adjust for age at enrollment, weight, ethnicity, smoking status, alcohol consumption, history of diabetes, total energy expenditure from recreational physical activity (MET-hours/week), self-reported number of falls in the previous 12 months, personal history of any fracture at the time of screening, calcium, vitamin D, bisphosphonate, and glucocorticoid use at screening.

[†] The interaction between age group at enrollment and time (natural log scale) was included due to evidence of non-proportionality.

Table 4

Estimated BMD comparisons

	Menopause age group comparison	Estimated difference (g/cm ²)	95% CI	<i>p</i>
*Whole body BMD comparisons	<40 <i>vs</i> 40–49	−0.03	(−0.07, −0.004)	0.03
	<40 <i>vs</i> 50	−0.05	(−0.08, −0.02)	<.01
	40–49 <i>vs</i> 50	−0.02	(−0.03, −0.004)	<.01
*Left hip BMD comparisons	<40 <i>vs</i> 40–49	−0.02	(−0.06, 0.02)	0.25
	<40 <i>vs</i> 50	−0.05	(−0.08, −0.01)	<.01
	40–49 <i>vs</i> 50	−0.03	(−0.04, −0.01)	<.01
*Total spine BMD comparisons	<40 <i>vs</i> 40–49	−0.09	(−0.15, −0.04)	<.01
	<40 <i>vs</i> 50	−0.11	(−0.16, −0.06)	<.01
	40–49 <i>vs</i> 50	−0.02	(−0.04, 0.003)	0.10

* Multivariable models adjust for age at enrollment; BMI; smoking status; alcohol consumption; history of DM; total energy expenditure (MET-hours/week); number of falls in the previous 12 months; history of any fracture at the time of screening; calcium, vitamin D, bisphosphonate, and glucocorticoid use; and DEXA scanner at screening.

Table 5

a) Number of fractures by age at menopause among WHI OS women with no TAH or BSO, no history of HT use and no self-reported HT use during follow-up (n=21,711)

Age at Menopause	N	Total no. of fractures (%)	Total no. of hip fractures (%)
<40	524	139 (26.5%)	17 (3.2%)
40 – 49	6,626	1,732 (26.1%)	188 (2.8%)
50 or older	14,561	3,898 (26.8%)	388 (2.7%)

b) Number of fractures by age at menopause among WHI OS women with no TAH or BSO, no history of HT use, no self-reported HT use during follow-up, and baseline whole body or left hip BMD measurements (n=1,351; a subset of above)

Age at Menopause	N	Total no. of fractures (%)	Total no. of hip fractures (%)
<40	44	10 (22.7%)	1 (2.3%)
40 – 49	444	124 (27.9%)	19 (4.3%)
50 or older	863	271 (31.4%)	30 (3.5%)

Chi-square p-values comparing total and hip fractures between menopause groups: p=0.63 and p= 0.59, respectively

Chi-square p-values comparing total and hip fractures between menopause groups: p=0.24 and p=0.67, respectively