Menopause: The Journal of The Menopause Society
Vol. 00, No. 00, pp. 00-00
DOI: 10.1097/GME.0000000000002272

ORIGINAL STUDY

Discontinuation of hormone therapy and bone mineral density: does physical activity modify that relationship?

Alyssa N. Sheedy, BS,[1] Jean Wactawski-Wende, PhD,[2] Kathleen M. Hovey, MS,[2] and Michael J. LaMonte, PhD, MPH[2]

Abstract

Objective: Hormone therapy can positively impact bone mineral density after menopause. We explored bone mineral density change in postmenopausal women who discontinued hormone therapy after the Women's Health Initiative landmark 2002 trial results were published. We secondarily explored whether usual physical activity modified the results.

Methods: Postmenopausal women participating in the Buffalo OsteoPerio study with information on hip bone density, hormone therapy use, and self-reported physical activity at two time points (1997-2001; 2002-2007) were included (N = 961). Hormone therapy included three groups according to use at baseline and year 5 (non/non; current/non; current/current).

Results: At baseline (mean age, 65.9 years; SD, 6.7 years), 480 women were not using hormone therapy, while 481 were current users. Between the baseline and 5-year visits, 336 women using hormone therapy discontinued. Baseline total hip bone density was highest in current users. After 5 years, those who continued hormone therapy exhibited no bone loss; those who discontinued exhibited the greatest loss at the total hip of −0.021 gm/cm^2. Women who never used hormone therapy exhibited some loss of −0.012 gm/cm^2. Usual physical activity did not appreciably impact change in bone density in any group.

Conclusions: This prospective observational study explored the 5-year change in bone mineral density among older postmenopausal women after the landmark 2002 hormone therapy trial findings were released. We found bone density decreased in never-users and in women who discontinued use. Bone density was maintained in current users. Although usual physical activity did not mitigate bone loss, targeted physical activity regimens should be investigated.

Key Words: Bone mineral density – Hormone therapy – Physical activity – Postmenopausal.

Menopause is defined as the cessation of menstrual cycles due to decline of follicular ovarian function and results in the onset of various expected physiological changes, including decreases in bone mineral density (BMD) due to declining ovarian estrogen production.[1] Estrogen is a naturally occurring physiological hormone that helps to control osteoclast activity. After menopause, BMD loss can occur because of drops in endogenous estrogen production, resulting is greater bone resorption by osteoclastic cells and reduction in new bone formation. As a result, postmenopausal women are at greater risk for experiencing significant drops in BMD and increasing their risk for the development of osteoporosis and bone fracture.[2]

Menopausal hormone therapy (HT) use in postmenopausal women can reduce bone loss. However, HT use in postmenopausal women has been met with hesitancy since the results of the Women's Health Initiative (WHI) estrogen plus progestin trial in 2002. The trial showed higher risk than benefit in older

Received June 27, 2023; revised and accepted August 31, 2023.
From the [1]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY; and [2]Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, NY.
Funding/support: Funding supporting this work includes U.S. Army Reserve Medical Corps grant 17-96-1-6319 and R01 DE13505. The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute through contract nos. 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005.
Financial disclosure/conflicts of interest: None reported.
Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).
Address correspondence to: Michael J. LaMonte, PhD, MPH, 270 Farber Hall, Buffalo, NY 14214. E-mail: mlamonte@buffalo.edu

women taking HT. The risks included heart disease, stroke, and breast cancer.[3] Hip and total fracture reductions, and bone density increases, were shown to be the major benefit of estrogen plus progestin.[4] However, discontinuation of HT use can result in bone loss similar to that which occurs at the time of menopause. BMD returns to pre-HT treatment levels after HT discontinuation.[5,6]

There is some evidence that certain types of sustained physical activity (PA) in women can provide benefit to BMD. Weight-bearing exercise and resistance training early in life have the greatest positive impact on improvements in BMD.[7] However, after menopause, PA can still help maintain BMD at specific bone sites, including the femoral neck, lumbar spine, and trochanter.[8] The relationship between PA and BMD in postmenopausal women over age 65 as explored by Pinheiro et al in their 2020 systematic review concluded that physical activity that is diverse in exercise types, specifically resistance training, plays a role in osteoporosis prevention.[9] The data indicated that the bone response may vary by body region and higher dose exercise programs are more effective. In addition findings from Gonzalo-Encabo et al in 400 postmenopausal women participating in a 12-month exercise intervention suggested that postmenopausal women could prevent some BMD loss with greater volumes of aerobic exercise, specifically those involving weight-bearing components.[10] Overall, this study suggested a dose-response effect for greater maintenance of BMD with higher PA levels.

The University at Buffalo served as a WHI Vanguard center, enrolling women into the study from 1993 to 1998. An ancillary investigation entitled the Buffalo Osteoporosis and Periodontal Disease (OsteoPerio) study started in 1997 and was designed to explore the relationship between osteoporosis and periodontal disease in postmenopausal women.[11] These participants had their BMD assessed longitudinally at two time points, baseline (1997-2001) and 5 years later (2002-2006). As such, assessment of BMD was conducted during the time frame when the 2002 WHI study findings were released. Use of HT in the United States reduced markedly at that time.[3] This provided the opportunity to assess the impact of HT discontinuation on BMD as part of an established prospective cohort study. BMD, HT use, and usual daily PA levels were all assessed as part of the OsteoPerio study, allowing us to look at the relationship of HT use discontinuation and BMD, and whether higher PA levels are associated with less BMD loss in women who discontinued HT use.

METHODS

Study population

Participants included women initially enrolled in the WHI Observational Study (OS) at the Buffalo, New York, clinical center between 1993 and 1998. The OsteoPerio study was funded to recruit women from WHI-OS about 3 years after initial WHI enrollment (1997-2001; OsteoPerio Study baseline). A follow-up study to look at change in osteoporosis and periodontal disease was conducted 5 years later (2002-2005).[11]

At OsteoPerio baseline, 1,342 participants were enrolled in the study and at the year 5 reexamination 1,026 of those women returned for a follow-up visit.[11] At each time point, women had their BMD assessed, completed a medication inventory, self-reported their usual daily PA levels, completed an oral health examination, and completed questionnaires on demographics, personal and family medical histories, and risk factors for osteoporosis and periodontal disease. The most frequent reason for not completing a year 5 examination was ineligibility (n = 102) and not interested (n = 151) with only a small number (n = 9) unable to contact (Fig. 1). We compared baseline characteristics between those who completed and did not complete a year-5 examination (Supplemental Table 1, http://links.lww.com/MENO/B170). Those who did not complete the examination were slightly older and had greater time since menopause, more likely to be a current smoker

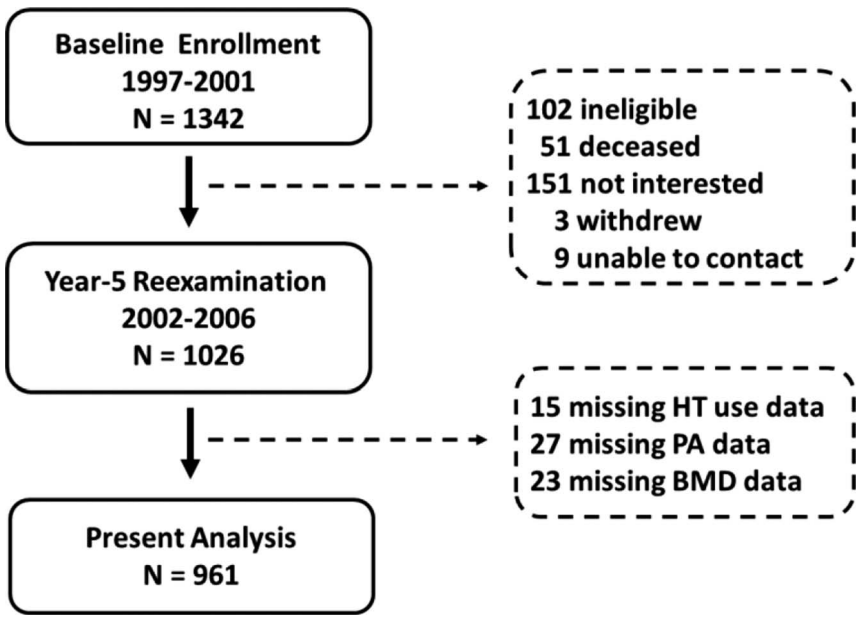

FIG. 1. Flowchart detailing the enrollment of participants into the Buffalo OsteoPerio Study and the present analysis.

and use bone medication, less likely to be a current HT user, and less physically active. Mean hip and femoral neck BMD were slightly lower in these women as well. For the present analysis, women were excluded who did not have a year 5 visit, were missing data on HT use, PA, or BMD at either time point for a final analytic sample of 961 women (Fig. 1).

Demographic and health characteristics were collected at baseline using standardized questionnaires and clinical assessments. This included age, body mass index (BMI; kg/m^2), attained education, neighborhood socioeconomic status (nSES), smoking history and pack-years, family history of osteoporosis, use medications known to affect bone density, vitamin D, and calcium supplementation use, years since menopause, years taking HT.

Hormone therapy use

Study participants were asked to bring to each clinical examination all their prescription medications and their over-the-counter medications in the original bottles. Details on specific medication names, doses, and length of use were recorded. For the present analysis, participants were divided into three categories depending on their HT use at OsteoPerio baseline and year 5 follow-up visit. The categories defined those who were not using HT at baseline or year 5 (nonuser/nonuser; n = 480), those who used HT at baseline but not at year 5 (current user/nonuser; n = 336), and those who used HT at both time points (current user/current user; n = 145). Participants who had discontinued HT use by the time of their year 5 follow-up were further categorized according to the number of years they had stopped taking HT before their year 5 visit.

Assessment of bone mineral density

We assessed BMD using dual-energy X-ray absorptiometry (DXA) scanning at the baseline visit (QDR-4500A; Hologic Inc., Beford, MA) and at the Year-5 follow-up visit (Discovery A; Hologic Inc., Bedford, MA). The present analysis includes BMD (g/cm^2) measures for the total hip and femoral neck regions. Standardized scanning protocols administered by calibrated DXA technicians enhanced quality of the BMD measures. In addition, we conducted repeated scans separated by 2 weeks in 20 volunteers to assess reproducibility of BMD measures. The coefficients of variation were <1%.

Assessment of physical activity

We summarized average total PA and average walking PA over all available assessments beginning at OsteoPerio baseline through the year 5 follow-up visit (99% of participants have ≥5 measures). PA was assessed similarly at both OsteoPerio time points and on annual health updates through the national WHI. Metabolic equivalent (MET) intensity values for the reported activities were multiplied by the number of hours per week reported by participants to create MET-hours/wk as a summary measure of usual PA levels.[12]

Statistical analysis

Participant baseline characteristics were summarized for the overall cohort and according to the three HT use categories. Analysis of variance was used to assess differences in BMD endpoints (continuous g/cm^2) according to HT use categories defined jointly by status at baseline and Year-5 examinations. Stratification of BMD over jointly categorized PA (tertiles) and HT use was conducted to determine whether the relationship between BMD and HT use differed by levels of total PA and walking PA. Analysis of covariance was used to control for specified covariates that were identified in the literature as being potentially relevant to an association between PA, HT use, and BMD. Effect modification was tested by including a multiplicative term (PA × HT use) in the model and a Wald test for interaction at alpha 0.05. Multivariable models included age, BMI, education, smoking history, family history of osteoporosis, use of bone medications, vitamin D, and calcium supplementation use. Models of 5-yr change in BMD also included baseline BMD to ensure baseline comparability given the observational study design. In a subanalysis, time since stopping HT prior to year 5 was further assessed in women who discontinued HT use. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 characterizes the 961 participants included in these analyses. Overall, participants on average were 65.9 years old, had a BMI of 26.5 kg/m^2 and tended to have a college education or more. More than half were never smokers (54.3%), and a small number were current smokers (2.4%). A total of 77 (8.0%) participants were on some form of bone modifying medication, 566 (58.9%) participants were on vitamin D supplementation and 691 (71.9%) participants were on some amount of calcium supplementation, usually as part of a multivitamin. A total of 481 (50.1%) of the total participants were on HT use at baseline (current/current and current/non-users) while the other 480 (49.9%) were never users of HT (nonuser/nonuser). In addition, most participants (71.7%) who stopped HT after their baseline visit (current/nonuser) did so within 2 years of their baseline visit.

Unadjusted BMD values at baseline and year 5 are presented according to HT use categories in Table 2. Mean hip BMD at baseline among women who were HT nonusers at both examinations was 0.840; and was 0.888 and 0.892 ($P < 0.001$ with nonusers, each) in those who were current/nonusers and current/current users at baseline and year 5 examinations, respectively. At Year-5, participants who were HT non-users had a mean hip BMD loss of 0.012 g/cm^2, whereas hip BMD loss was less in those who discontinued HT use (current/nonuser) and those who were HT users at both examinations (0.021 g/cm^2 and 0.000 g/cm^2 loss, respectively; $P < 0.05$ with HT nonusers). Participants who were HT users at both time points showed virtually no change in total hip BMD.

We next assessed whether the change in hip BMD across the three HT use groups was modified by the amount of usual total PA or walking PA (Table 3) reported by these women.

There was no clear evidence that the unadjusted mean loss of hip BMD at Year-5 differed by total PA level (BMD change, interaction $P = 0.06$) or walking PA (interaction $P = 0.133$). Multivariable-adjusted models yielded similar results (Supplemental Table 2, http://links.lww.com/MENO/B170).

Further examining the subcohort of participants that discontinued HT use prior to the year 5 exam (n = 329; Table 4), a total of 124 (37.7%) participants stopped HT use less than 1 year before their 5-year visit, 111 (33.7%) participants stopped within 1 to

TABLE 1. *Baseline participant characteristics by HT use status at baseline and year 5 (Baseline/Year 5)*

Characteristics	Overall (N = 961)	HT Use at Baseline/Year 5		
		Nonuser/Nonuser (n = 480)	Current/Nonuser (n = 336)	Current/Current (n = 145)
Age at baseline: mean (SD), y	65.9 (6.7)	67.2 (6.8)	64.8 (6.3)	64.1 (6.2)
Younger than 65 y, n (%)	463 (48.2)	192 (40.0)	186 (55.4)	85 (58.6)
65-70 y	258 (26.9)	134 (27.9)	88 (26.2)	36 (24.8)
Older than 70 y	240 (25.0)	154 (32.1)	62 (18.4)	24 (16.6)
BMI (kg/m^2), mean (SD)	26.5 (5.1)	27.1 (5.5)	26.1 (4.6)	25.6 (4.6)
nSES, mean (SD)	76.2 (6.9)	75.8 (7.0)	76.4 (7.2)	77.0 (5.8)
Education, n (%)				
High School	200 (21.2)	115 (24.3)	56 (17.0)	29 (20.6)
College	408 (43.2)	211 (44.5)	151 (45.9)	46 (32.6)
Postcollage	336 (35.0)	148 (31.2)	122 (37.1)	66 (46.8)
Years since menopause, mean (SD)	17.9 (8.4)	18.9 (8.6)	16.9 (7.9)	17.1 (8.4)
Years taking HT, mean (SD)	5.6 (7.2)	1.3 (3.7)	8.9 (6.4)	12.2 (8.4)
Smoking, n (%)				
Never	522 (54.3)	267 (55.6)	172 (51.2)	83 (57.2)
Former	416 (43.3)	197 (41.0)	158 (47.0)	61 (42.1)
Current	23 (2.4)	16 (3.3)	6 (1.8)	1 (0.7)
Pack-years smoking, mean (SD)	9.4 (17.3)	9.8 (17.7)	9.8 (17.6)	7.2 (15.0)
Family history[a] of osteoporosis, n (%)	220 (22.9)	96 (20.0)	88 (26.2)	36 (24.8)
Bone medication use[b], n (%)	77 (8.0)	54 (11.3)	14 (4.2)	9 (6.2)
Vitamin D supplement, n (%)	566 (58.9)	277 (57.7)	202 (60.1)	87 (60.0)
Calcium supplement, n (%)	691 (71.9)	333 (69.4)	250 (74.4)	108 (74.5)
Physical activity (MET-h/wk),[c] mean (SD)				
Total activity	14.3 (12.0)	14.3 (12.2)	14.0 (11.9)	15.1 (11.8)
Walking activity	4.1 (4.6)	4.0 (4.5)	4.1 (4.5)	4.5 (4.7)
Years since stopping HT[d] at 5 y, n (%)	N/A	N/A		N/A
Less than 1 y			127 (37.8)	
1 to < 2 y			114 (33.9)	
Greater than 2 y			95 (28.3)	

BMI, body mass index; HT, menopausal hormone therapy; MET, metabolic equivalent; nSES, neighborhood socioeconomic status; SD, standard deviation.
[a]Family includes mother, father, siblings, and children.
[b]Medications reported for osteoporosis, Fosamax, Evista, Actonel, Miacalcin, Forteo, Boniva, Alendronate, Risedronate.
[c]MET hours/wk baseline to 5-yr cumulative average.
[d]Years since last took in those who stopped taking HT during follow-up.

2 years, and 94 (28.6%) participants stopped more than 2 years before their 5-year visit. By the Year-5 visit, while all participants experienced hip BMD loss overall, the greatest mean loss in BMD was for those who discontinued HT use early during the time interval at 1 to 2 years and >2 years prior to year 5 (0.025 g/cm^2, both) as compared with <1 year (0.012 g/cm^2 loss; $P < 0.05$ each). Assessment of whether PA level modified the change in hip BMD associated with time since stopping HT use is given in Table 5. There was no significant difference in unadjusted mean hip BMD loss across either total PA (interaction $P = 0.265$) or walking PA (interaction $P = 0.196$). Similar results were obtained from multivariable-adjusted analyses (Supplemental Table 3, http://links.lww.com/MENO/B170).

TABLE 2. *Unadjusted mean hip BMD (g/cm^2) at baseline and Year-5 according to HT use at each time point*

	HT Use at Baseline/Year 5			
	Nonuser/Nonuser (n = 480)	Current/nonuser (n = 336)	Current/Current (n = 145)	P[a]
	Mean (SD)	Mean (SD)	Mean (SD)	
Baseline	0.840 (0.132)	0.888 (0.134)	0.892 (0.131)	
Year 5	0.829 (0.132)	0.867 (0.129)	0.892 (0.131)	
BMD change	−0.012 (0.039)	−0.021 (0.036)[b]	0.000 (0.030)[b]	<0.001

BMD, bone mineral density; HT, menopausal hormone therapy; SD, standard deviation.
[a]F test P value.
[b]$P < 0.05$ when compared with nonuser/nonuser.

Results for analysis of femoral neck BMD are given in Supplemental Tables 4-9 (http://links.lww.com/MENO/B170). Mean loss of femoral neck BMD was significantly greater for women who discontinued HT use (current/non-user) compared with those who were either HT non-users or current users at both examinations ($P < 0.05$; Supplemental Table 4, http://links.lww.com/MENO/B170). Neither total PA nor walking PA modified the 5-Year change in mean femoral neck BMD in unadjusted (Supplemental Table 5, http://links.lww.com/MENO/B170) or multivariable adjusted (Supplemental Table 6, http://links.lww.com/MENO/B170) models (interaction $P > 0.05$, all). Mean femoral neck BMD loss was greatest for those who discontinued HT use 1 to 2 years and >2 years before year-5 (0.018 and 0.025 g/cm^2 loss, respectively; Supplemental Table 7, http://links.lww.com/MENO/B170) as compared to those who discontinued <1 year before year 5 (0.001 g/cm^2 loss; $P < 0.05$ each). There was no clear evidence of effect modification by total PA or walking PA on the association between 5-year femoral neck BMD change and time since stopping HT use in either unadjusted (Supplemental Table 8, http://links.lww.com/MENO/B170) or multivariable-adjusted (Supplemental Table 9, http://links.lww.com/MENO/B170) models (interaction $P > 0.05$, all).

DISCUSSION

Clear and strong evidence for menopausal HT to benefit BMD in postmenopausal women was demonstrated in the Women's

TABLE 3. *Unadjusted mean hip BMD (g/cm^2) according to HT use at baseline and Year-5 stratified on PA level*

		HT use at baseline/Year-5			
	Total PA (MET-h/wk)[a]	Nonuser/Nonuser, Mean (SD)	Current/Nonuser, Mean (SD)	Current/ Current, Mean (SD)	Interaction P^b
Baseline	<7.4	0.844 (0.135)	0.891 (0.142)	0.912 (0.136)	0.656
	≥7.4-16.7	0.838 (0.130)	0.890 (0.126)	0.868 (0.118)	
	≥16.7	0.838 (0.133)	0.882 (0.136)	0.900 (0.139)	
Year 5	<7.4	0.828 (0.136)	0.869 (0.135)	0.922 (0.141)	0.060
	≥7.4-16.7	0.828 (0.132)	0.870 (0.118)	0.863 (0.113)	
	≥16.7	0.830 (0.128)	0.862 (0.134)	0.897 (0.137)	
BMD change	<7.4	−0.016 (0.047)	−0.022 (0.039)	0.010 (0.029)	0.060
	≥7.4-16.7	−0.010 (0.037)	−0.020 (0.034)	−0.004 (0.031)	
	≥16.7	−0.008 (0.029)	−0.020 (0.035)	−0.003 (0.028)	
	Walking PA (MET-hours/wk)[a]				
Baseline	<1.1	0.859 (0.138)	0.886 (0.147)	0.894 (0.147)	0.180
	≥1.1-4.7	0.825 (0.135)	0.894 (0.127)	0.867 (0.102)	
	≥4.7	0.835 (0.122)	0.884 (0.130)	0.916 (0.139)	
Year 5	<1.1	0.841 (0.137)	0.866 (0.138)	0.897 (0.153)	0.133
	≥1.1-4.7	0.817 (0.137)	0.875 (0.123)	0.873 (0.097)	
	≥4.7	0.827 (0.121)	0.860 (0.126)	0.908 (0.139)	
BMD change	<1.1	−0.018 (0.046)	−0.020 (0.040)	0.003 (0.034)	0.133
	≥1.1-4.7	−0.008 (0.036)	−0.018 (0.035)	0.006 (0.028)	
	≥4.7	−0.008 (0.031)	−0.023 (0.032)	−0.008 (0.027)	

BMD, bone mineral density; HT, menopausal hormone therapy; MET, metabolic equivalent; PA, physical activity; SD, standard deviation.
[a]MET-h/wk baseline to Year-5 cumulative average, 99% have ≥5 measures.
[b]*P* value for Wald interaction test based on model cross-product-term (HT use × PA level).

Health Initiative HT trials.[4,13] Despite the benefit on bone health, the overall risks for adverse outcomes outweighed the overall benefits and the HT trials were terminated early.[3,14] Soon after publication of the WHI HT trial results, use of menopausal HT dropped precipitously in US women including discontinuation of use among women who had previously been on HT.[15] Only limited understanding is available regarding the impact that discontinuing HT has on short-term BMD status. In the WHI HT trials there was a relatively rapid response in total hip BMD by the end of year 1 (mean increase ≈2%) and end of year 3 (mean increase ≈4%) among the active treatment arms.[4,13] Based on this and previous literature, one might similarly expect a rapid reduction in BMD soon after HT discontinuation. In our present study, hip BMD was 0.888 and 0.867 gm/cm^2, respectively, in women who were HT users at baseline that discontinued during 5-Year follow-up. This reflects a 2.4% reduction in hip BMD for women who stopped HT use during the 5-year interval. In another study on postmenopausal women who initially took oral conjugated estrogen (0.625 mg/d) for 2 years and then discontinued use, trochanteric BMD reduced by 2.4% during a subsequent three-year follow-up,[16] which is quite consistent with our current observational study result. Alterations in biochemical markers of bone turnover subsequent to discontinuing menopausal HT use could partly explain the associated loss of bone mineral density.[17]

Exercise training interventions have been shown to attenuate loss of BMD in postmenopausal women.[18-20] One previous randomized controlled trial found that the combined effect of exercise and HT use was superior than exercise alone in slowing the rate of forearm BMD loss in postmenopausal women.[19] The exercise intervention in previous randomized trials typically has been administered in a supervised setting and included strengthening exercise and high impact training which might not fully generalize to free-living settings.

The impact that usual daily PA might have on BMD loss, as investigated in our current study, is less understood. Cross-sectional data indicate PA is positively associated with total hip and femoral neck BMD in US women 50 years and older participating in the National Health and Nutrition Examination Survey[21] and in the Women's Health Initiative.[22] Longitudinal data from an observational cohort on the menopausal transition showed that increased leisure-time PA over two assessments was associated with a lower rate of loss in femoral neck BMD.[23]

To our knowledge there are no published findings describing the influence of usual PA on BMD loss immediately following discontinuation of menopausal HT. In our longitudinal study herein, we tested the hypothesis that higher levels of self-reported usual total PA and walking PA would be associated with lower 5-year loss of hip and femoral neck BMD in older postmenopausal women who initially were HT users but discontinued following the results of the WHI HT trials. Total PA averaged over available assessments from baseline to year 5 were somewhat lower in HT (baseline/year 5) users/nonusers (14.0 MET-h/wk) as compared to nonusers/nonusers (14.3 MET-h/wk) and users/users (15.1 MET-h/wk). However, even though women who were initially HT users and discontinued use during the 5-year interval experienced 2.4% loss in hip BMD (baseline: 0.888 vs year 5: 0.867 gm/cm^2), there was no significant difference in loss of

TABLE 4. *Unadjusted mean hip BMD (g/cm^2) by years since stopping HT before Year-5 visit in who discontinued HT use (n = 329)*

	Years since stopping HT use before Year-5 examination			
	<1 yr (n = 124)	1-2 yr (n = 111)	>2 yr (n = 94)	P^a
	Mean (SD)	Mean (SD)	Mean (SD)	
Baseline	0.877 (0.124)	0.897 (0.135)	0.890 (0.145)	
5-yr	0.864 (0.125)	0.871 (0.128)	0.865 (0.135)	
BMD change	−0.012 (0.031)	−0.025 (0.037)[b]	−0.025 (0.038)[b]	0.006

BMD, bone mineral density; HT, menopausal hormone therapy; SD, standard deviation.
[a]F-test *P* value.
[b]$P < 0.05$ when compared with <1 yr.

TABLE 5. *Unadjusted mean hip BMD (g/cm^2) according to years since stopping HT before Year-5 visit stratified on PA level (n = 329)*

		Years Since Stopping HT Use Before Year 5 examination			Interaction, P^b
		<1 yr	1-2 yr	>2 yr	
		Mean (SD)	Mean (SD)	Mean (SD)	
	Total PA (MET-hours/wk)[a]				
Baseline	<7.4	0.882 (0.119)	0.901 (0.145)	0.891 (0.169)	0.601
	≥7.4-16.7	0.871 (0.127)	0.916 (0.109)	0.877 (0.142)	
	≥16.7	0.876 (0.129)	0.869 (0.150)	0.901 (0.128)	
5 y	<7.4	0.863 (0.118)	0.875 (0.140)	0.869 (0.156)	0.265
	≥7.4-16.7	0.866 (0.123)	0.885 (0.104)	0.850 (0.129)	
	≥16.7	0.863 (0.140)	0.852 (0.143)	0.873 (0.124)	
BMD change	<7.4	−0.019 (0.031)	−0.026 (0.038)	−0.021 (0.050)	0.265
	≥7.4-16.7	−0.006 (0.027)	−0.031 (0.040)	−0.026 (0.028)	
	≥16.7	−0.014 (0.036)	−0.017 (0.030)	−0.028 (0.035)	
	Walking PA (MET-h/wk)[a]				
Baseline	<1.1	0.874 (0.125)	0.900 (0.140)	0.880 (0.174)	0.952
	≥1.1-4.7	0.880 (0.113)	0.904 (0.135)	0.915 (0.141)	
	≥4.7	0.874 (0.140)	0.889 (0.133)	0.881 (0.118)	
5 y	<1.1	0.857 (0.125)	0.876 (0.132)	0.861 (0.159)	0.196
	≥1.1-4.7	0.867 (0.113)	0.879 (0.136)	0.894 (0.131)	
	≥4.7	0.868 (0.145)	0.863 (0.123)	0.846 (0.113)	
BMD change	<1.1	−0.017 (0.030)	−0.024 (0.041)	−0.019 (0.048)	0.196
	≥1.1-4.7	−0.014 (0.034)	−0.025 (0.035)	−0.021 (0.037)	
	≥4.7	−0.006 (0.026)	−0.026 (0.036)	−0.034 (0.027)	

BMD, bone mineral density; HT, menopausal hormone therapy; MET, metabolic equivalent; PA, physical activity; SD, standard deviation.
[a]MET-h/wk baseline to Year-5 cumulative average, 99% have ≥5 measures.
[b]*P* value for Wald interaction test based on model cross-product-term (HT use × PA level).

BMD across incremental tertiles of total PA (comparing Tertile 1 to 3: 2.4%, 2.3%, 2.3%; Table 3), nor was there a significant interaction of total PA and HT status on longitudinal change in hip BMD (multivariable interaction, $P = 0.131$; Supplemental Table 2, http://links.lww.com/MENO/B170). The findings for usual walking PA and hip BMD (Table 3), and for total and walking PA with femoral neck BMD (Supplemental Tables 5-6, http://links.lww.com/MENO/B170) were similar to the results for total PA and hip BMD. We explored whether number of years since stopping HT use (<1, 1-2, >2 years) before the Year-5 BMD assessment influenced the primary results; however, there was no significant interaction between total PA and years since stopping on 5-year BMD change (Table 5, Supplemental Tables 3, 8, 9, http://links.lww.com/MENO/B170).

It is not entirely clear why study results did not support our hypothesis that higher usual PA levels would attenuate the 5-year loss of hip or femoral neck BMD in older ambulatory postmenopausal women selected from the community setting. One possibility is that the observational study design and relatively small sample size limited our ability to sufficiently test the hypothesis of interest. Women in our OsteoPerio study had, on average, reasonably high BMD at baseline and were relatively highly active and remained so during the 5-year follow-up. Greater variation in PA, as well as engagement in purposive higher impact activities,[18] might be required to mitigate loss of BMD among those women with higher loss due HT discontinuation. Additional research is needed to further understand whether PA is an effective modality to offset postmenopausal bone loss in women who discontinue HT, as HT use might be prescribed short-term in certain women for vasomotor symptom management,[24] and to better characterize the type and amount of PA for optimal benefit on BMD and other aspects of bone health in aging women. This could enhance future versions of national PA guidelines,[25] which currently provide only limited coverage regarding bone health in older women.

The present findings, however, do align with other related literature. Azimi-Shomali et al suggested that usual PA alone without intentionally increasing total PA has no effect on BMD biomarkers except calcium.[26] Yong-Sheng et al concluded that actively increasing long-term brisk walking had a positive effect on BMD in premenopausal women.[27] This suggests that PA changes likely need to be intentionally increased for BMD effects to be seen. Since the present study examined the data already collected from the OsteoPerio observational cohort study, no PA intervention was implemented. If a specific physical activity-based intervention or program was setup for the participants to actively follow, the mitigation of PA on 5-year bone loss may have been evident.

Our study has strengths providing insights relevant to women going through menopause who are concerned about associated bone loss. To the best of our knowledge, we are the only study that has attempted to analyze how usual PA levels might mitigate BMD loss during the initial years following stopping of the WHI hormone trial, where a vast number of women subsequently discontinued HT use. Many studies have previously examined the relationship between PA and BMD but not with the additional effect of HT use and subsequent discontinuation. The present results did not clearly support a role for usual daily PA to offset BMD loss associated with HT discontinuation. Additional data on this issue would be valuable in confirming or refuting our findings.

Second, the longitudinal data collected over a 5-year timeline is invaluable. Many published studies lack prospective follow-up on such a large number of participants where repeated assessments of BMD, PA, and HT use status are available. In addition, the postmenopausal age group is more vulnerable to changes in BMD, making this study population clinically relevant to examine further

in the hopes of finding ways to mitigate the inevitable changes in BMD brought upon by menopause.

There are study limitations to also consider. We were not able to characterize adherence to prescribed HT during the intervening years between baseline and Year-5 examinations, so it is possible that among current/current users there might have been disrupted HT use. Another limitation was the age range examined. With a mean age of 65.9 years old, many participants were beyond the immediate years directly following menopause which is known to be the period where the sharpest decline in BMD occurs.[2] This timeframe early in the menopause transition was captured in the ACTLIFE-RCT by Hettchen et al showing a positive impact of PA on BMD.[28] The early postmenopausal time interval might be a missed window of opportunity where PA could have a significant effect in mitigating bone loss with HT discontinuation. We were not able to specifically examine this menopause timing effect of PA on bone health in the present study. Additionally, designing a specific PA regimen for participants to follow after discontinuing HT would allow for a clearer exploration of the potential mitigating effects on bone loss.

CONCLUSION

In our prospective epidemiological cohort study, postmenopausal women who stopped HT use over a 5-year period appeared to lose total hip and femoral neck BMD at an accelerated rate when compared to those that never used or continued to use HT. Usual daily PA, including walking, did not appear to mitigate this BMD loss associated with HT discontinuation over a 5-year period. The potential effect that targeted PA regimens have on BMD loss in older postmenopausal women warrants further investigation.

Acknowledgments: We would like to thank the Women's Health Initiative and Buffalo OsteoPerio Study research participants and study staff for their dedication to these studies and to the health of women for generations to come.

REFERENCES

1. Kim MJ, Cho J, Ahn Y, Yim G, Park HY. Association between physical activity and menopausal symptoms in perimenopausal women. *BMC Womens Health* 2014;14:122. doi: 10.1186/1472-6874-14-122
2. Lupsa BC, Insogna K. Bone Health and Osteoporosis. *Endocrinol Metab Clin N Am* 2015;44:517-530. doi: 10.1016/j.ecl.2015.05.002
3. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333. doi: 10.1001/jama.288.3.321
4. Cauley JA, Robbins J, Chen Z, et al. Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729-1738. doi: 10.1001/jama.290.13.1729
5. Gatti D, Fassio A. Pharmacological management of osteoporosis in postmenopausal women: the current state of the art. *J Popul Ther Clin Pharmacol* 2019;26:e1-e17. doi: 10.15586/jptcp.v26.i4.646
6. Trémollieres FA, Pouilles JM, Ribot C. Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women. *Osteoporos Int* 2001;12:385-390. doi: 10.1007/s001980170107
7. Troy KL, Mancuso ME, Butler TA, Johnson JE. Exercise early and often: effects of physical activity and exercise on women's bone health. *Int J Environ Res Public Health* 2018;15:878. doi: 10.3390/ijerph15050878
8. Hejazi K, Askari R, Hofmeister M. Effects of physical exercise on bone mineral density in older postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. *Arch Osteoporos* 2022;17:102. doi: 10.1007/s11657-022-01140-7
9. Pinheiro MB, Oliveira J, Bauman A, Fairhall N, Kwok W, Sherrington C. Evidence on physical activity and osteoporosis prevention for people aged 65+ years: a systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. *Int J Behav Nutr Phys Act* 2020;17:150. doi: 10.1186/s12966-020-01040-4
10. Gonzalo-Encabo P, McNeil J, Boyne DJ, Courneya KS, Friedenreich CM. Dose-response effects of exercise on bone mineral density and content in post-menopausal women. *Scand J Med Sci Sports* 2019;29:1121-1129. doi: 10.1111/sms.13443
11. Banack HR, Genco RJ, LaMonte MJ, et al, OsteoPerio Study Group. Cohort profile: the Buffalo OsteoPerio microbiome prospective cohort study. *BMJ Open* 2018;8:e024263. doi: 10.1136/bmjopen-2018-024263
12. LaMonte MJ, Wactawski-Wende J, Larson JC, et al, Women's Health Initiative (WHI). Association of Physical Activity and Fracture Risk Among Postmenopausal Women. *JAMA Netw Open* 2019;2:e1914084. doi: 10.1001/jamanetworkopen.2019.14084
13. Jackson RD, Wactawski-Wende J, LaCroix AZ, et al, Women's Health Initiative Investigators. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. *J Bone Miner Res* 2006;21:817-828. doi: 10.1359/jbmr.060312
14. Manson JE, Kaunitz AM. Menopause management—getting clinical care back on track. *N Engl J Med* 2016;374:803-806. doi: 10.1056/NEJMp1514242
15. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:3975-4011. doi: 10.1210/jc.2015-2236
16. Greenspan SL, Emkey RD, Bone HG, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:875-883. doi: 10.7326/0003-4819-137-11-200212030-00008
17. Miller PD, Baran DT, Bilezikian JP, et al. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. *J Clin Densitom* 1999;2:323-342. doi: 10.1385/jcd:2:3:323
18. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int* 1999;9:1-12. doi: 10.1007/s001980050109
19. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med* 1991;325:1189-1195. doi: 10.1056/NEJM199110243251701
20. Korpelainen R, Keinänen-Kiukaanniemi S, Heikkinen J, Väänänen K, Korpelainen J. Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomized controlled 30-month intervention. *Osteoporos Int* 2006;17:109-118. doi: 10.1007/s00198-005-1924-2
21. Jain RK, Vokes T. Physical activity as measured by accelerometer in NHANES 2005-2006 is associated with better bone density and trabecular bone score in older adults. *Arch Osteoporos* 2019;14:29. doi: 10.1007/s11657-019-0583-4
22. Beck TJ, Kohlmeier LA, Petit MA, et al. Confounders in the association between exercise and femur bone in postmenopausal women. *Med Sci Sports Exerc* 2011;43:80-89. doi: 10.1249/MSS.0b013e3181e57bab
23. Greendale GA, Jackson NJ, Shieh A, et al. Leisure time physical activity and bone mineral density preservation during the menopause transition and postmenopause: a longitudinal cohort analysis from the Study of Women's Health Across the Nation (SWAN). *Lancet Reg Health Am* 2023;21:100481. doi: 10.1016/j.lana.2023.100481
24. Crandall CJ, Mehta JM, Manson JE. Management of menopausal symptoms: a review. *JAMA* 2023;329:405-420. doi: 10.1001/jama.2022.24140
25. *Physical Activity Guidelines for Americans (PAGA)*. 2nd ed,. Washington, DC: US Department of Health and Human Services; 2018
26. Azimi-Shomali S, Farshbaf-Khalili A, Eslamian F, Dolatkhah N, Ghassab-Abdollahi N. The relationship between usual daily physical activity with serum markers related to bone metabolism and demographic characteristics in postmenopausal women aged 50-65 years. *J Phys Act Health* 2022;19:417-424. doi: 10.1123/jpah.2021-0495
27. Lan YS, Feng YJ. The volume of brisk walking is the key determinant of BMD improvement in premenopausal women. *PLoS One* 2022;17:e0265250. doi: 10.1371/journal.pone.0265250
28. Hettchen M, von Stengel S, Kohl M, et al. Changes in menopausal risk factors in early postmenopausal osteopenic women after 13 months of high-intensity exercise: the randomized controlled ACTLIFE-RCT. *Clin Interv Aging* 2021;16:83-96. doi: 10.2147/CIA.S283177