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Surgical Menopause and Nonvertebral Fracture Risk among Older U.S. Women

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Abstract

Objective—To determine whether older postmenopausal women with a history of bilateral oophorectomy prior to natural menopause (surgical menopause) have a higher risk of nonvertebral, postmenopausal fracture than women with natural menopause.

Methods—We used 21 years of prospectively collected incident fracture data from the ongoing Study of Osteoporotic Fractures (SOF), a cohort study of community dwelling women without previous bilateral hip fracture who were age 65 or older at enrollment, to determine the risk of hip, wrist, and any nonvertebral fracture. Chi square and t-tests were used to compare the two groups on important characteristics. Multivariable Cox proportional hazards regression models stratified by baseline oral estrogen use status were used to estimate the risk of fracture.

Results—Baseline characteristics differed significantly between the 6,616 women within SOF who underwent either surgical (1,157) or natural (5,459) menopause, including mean age at menopause (44.3 ±7.4 versus 48.9 ±4.9 years, p<.001) and current use of oral estrogen (30.2% vs 6.5%, p<.001). Fracture rates were not significantly increased for surgical versus natural menopause, even among women who had never used oral estrogen (hip fracture, hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.63–1.21; wrist fracture HR 1.10, 95% CI 0.78–1.57; any nonvertebral fracture HR 1.11, 95% CI 0.93–1.32).

Conclusion—These data provide some reassurance that the long-term risk of nonvertebral fracture is not substantially increased for postmenopausal women who experienced premenopausal

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bilateral oophorectomy, compared to postmenopausal women with intact ovaries, even in the absence of postmenopausal estrogen therapy.

Database search terms

menopause; fracture; oophorectomy

Introduction

Among women of reproductive age in the United States, hysterectomy is the second most frequently performed surgical procedure after cesarean section. About 20 million US women have had a hysterectomy, and about 600,000 hysterectomies are performed annually (1). According to recent estimates, nearly 40% of women aged 15–44 years who undergo hysterectomy also have bilateral oophorectomy (1; 2).

While several studies have suggested an association between early menopause and decreased bone mineral density (BMD) and an increased risk for osteoporosis (3), no prospective cohort studies have assessed the impact of surgical menopause on long-term fracture risk. Therefore, we investigated whether women who underwent premenopausal bilateral oophorectomy (surgical menopause) were at increased risk of nonvertebral fracture compared with women who experienced natural menopause. We further evaluated whether observed associations of these surgeries with fracture risk were modified by postmenopausal oral estrogen therapy. We hypothesized that older women with a history of surgical menopause would have a higher risk of nonvertebral fracture than those without surgical menopause, and that this risk would be diminished by the use of oral estrogen.

Methods

We evaluated the effects of premenopausal bilateral oophorectomy (with or without hysterectomy) prior to menopause on fracture risk in comparison to natural menopause using data collected through August 2007 from the ongoing Study of Osteoporotic Fractures (SOF). SOF is a multi-center prospective study of risk factors for fracture in 9704 community dwelling white women 65 years of age or older enrolled into the cohort from 1986 to 1988 (4). Women were recruited irrespective of their BMD status or fracture history and were excluded only if they had undergone bilateral hip replacement or were unable to walk without the help of another person. All women provided written informed consent and the Institutional Review Boards at each site approved this study.

Participants were asked at baseline to provide their age at the time of their last natural menstrual period and at the time of oophorectomy and/or hysterectomy, if applicable. Participants were asked whether they still had menses after their hysterectomy to confirm hysterectomy status. From this information we defined 4 menopausal groups: 1) menopause resulting from premenopausal bilateral oophorectomy (surgical menopause, n=1157) with or without hysterectomy; 2) premenopausal hysterectomy without simultaneous bilateral oophorectomy (n=1679), which included women with no ovaries removed, one ovary removed, uncertainty about ovarian status, or bilateral oophorectomy performed at a later date; 3) natural menopause with a history of oophorectomy or hysterectomy (n=1288); and 4) natural menopause without previous oophorectomy or hysterectomy (n=5459, referent). We excluded women who could not confirm whether their hysterectomy occurred before or after menstrual cessation (n=1), who did not know if they had had a hysterectomy (n=18), or who did not provide any information about menopause (n=102) from the analyses. Evaluation of fracture risk among women with postmenopausal oophorectomy in this cohort has previously been performed and no increased risk of fracture was found (5). Therefore,

for this analysis we excluded women with natural menopause who had postmenopausal hysterectomy or oophorectomy. Because the time of menopause could not be ascertained for women without bilateral oophorectomy at the time of hysterectomy, this group was also excluded from the primary analyses, yielding a final cohort for analysis of 6,616 women with surgical or natural menopause.

The primary fractures of interest for this study were incident hip, wrist, and any nontraumatic, nonvertebral fracture. Fractures resulting from major trauma were excluded. Study participants have been contacted by mail or telephone every four months to identify the occurrence of fractures (more than 95% complete to date). Incident fractures were verified by physician review of radiology reports.

Information was collected from all participants at baseline by questionnaire, review of medication bottles, food intake diaries, and physical exam. Baseline characteristics of primary interest included age at baseline and menopause, calcium and alcohol intake, tobacco use, obstetrical history (parity and breastfeeding), medical history (diabetes, self-reported health, and fracture since age of 50, height at age 25), maternal history of fracture, medications (oral estrogen and long-acting benzodiazepines), activity level (evaluated as time spent on feet during the day), and physical measures (pulse, weight, depth perception, contrast sensitivity, and BMD). These characteristics were chosen because they have been associated with fracture risk.(4; 6; 7) Bone mineral density (BMD) measurements of the distal radius and calcaneus were performed at baseline by single photon absorptiometry using OsteoAnalyzers (Siemens-Osteon, Wahiawa, Hawaii); whereas, ascertainment of BMD of the proximal femur by dual energy x-ray absorptiometry (DXA) (QDR 1000, Hologic, Waltham, MA) was first performed at the second study visit, between 1988 and 1990, for the 8074 women surviving at that time. Age at menopause was considered unknown or missing for women who experienced natural menopause, but could not recall their age when it occurred (n=77). All covariates included in multivariate models were from the baseline exam, except oral estrogen use. Estrogen use was updated about every two years at each study visit, and these data were used to determine continuous use or nonuse of oral estrogen for each participant.

Statistical analyses

T-tests for continuous variables and Pearson chi-square tests for categorical variables were used to assess differences in baseline characteristics between the menopause groups. Cox proportional hazards regression models were used to estimate the risk of fracture (hazard ratio, [HR], 95% confidence interval [CI]). Time to fracture was defined as the time from baseline to the first hip, wrist, or nonvertebral fracture. Women who did not have a fracture or died prior to fracture were censored at the time of death or at the time of their last available follow-up questionnaire. Recently published data suggest that traumatic fractures should also be included as outcomes in observational studies (8). Given our decision to exclude women with traumatic fractures, we performed a sensitivity analysis including women in the SOF cohort who had traumatic fractures, and the results were unchanged.

Multivariable regression models were developed to provide relative risk estimates of fracture. The models were stratified by estrogen use as there was a significant interaction between menopause type and estrogen use status. For analyses among never and past users of oral estrogen, those who began using estrogen during follow-up were censored at the time they first reported estrogen use (including 28 never users with hip fracture, 21 with wrist fracture, and 78 with any nonvertebral fracture, and 37 past users with hip fracture, 27 with wrist fracture, and 91 with any nonvertebral fracture). For analyses among current users of estrogen, those who discontinued estrogen use were censored at the time they reported that

they stopped taking this medication (including 38 women with hip fracture, 18 with wrist fracture, and 99 with any nonvertebral fracture). Women with missing estrogen data at a specific study visit were assigned the same status as at their previous visit.

The stratified models were then adjusted for all characteristics that differed significantly between the two menopause groups. To determine the impact of BMD on the relationship between menopause and fracture, BMD was added last to the multivariable models and the results are reported separately. Because DXA was not performed until the second SOF clinic visit we used baseline BMD measures for the models (calcaneal BMD for hip and any nonvertebral fracture models and distal radius for wrist fracture models). Previous studies among the SOF cohort have demonstrated that appendicular bone density measures are strong predictors of nonvertebral fractures (9; 10).

All p-values were based on two-sided tests of significance and a p-value of <0.05 was considered statistically significant for our analyses. Statistical analyses were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

Results

Baseline characteristics of the 6,616 women included in the analysis varied considerably by menopause type, and those that differed significantly are shown in Table 1. Women with a history of surgical menopause were younger at enrollment (70.8 vs. 71.7 years, p<.001), weighed more (67.8 vs. 66.7 kg, p=.01), and had a higher mean calcium intake (2,942 mg/week vs. 2,640 mg/week, p=.03). Among women with a history of surgical menopause, 62.2% were current or past users of oral estrogen, which was about twice that of women with natural menopause (31.7%, p<.001). Therefore, it is not surprising that women with a history of surgical menopause also had higher mean BMD measures at all sites (p<.001, Table 1). Only 0.15% (n=14) reported ever using an estrogen patch. The menopause groups did not differ in parity, activity levels (evaluated as ≤ 4 hours on feet daily), maternal history of hip fracture, personal history of fracture since age 50, height at age 25, and pulse, or in smoking status (current, past, or never); however, the mean pack-year history among current or past smokers was higher for the surgical menopause group (12.5 vs. 10.7 pack-years, p=.01).

During a mean follow-up of 14.3 years (SD=5.4, range 0.02–20.6 years), 2,697 nontraumatic, nonvertebral fractures were identified of which there were 909 hip and 669 wrist fractures. Age-adjusted incidence rates of fracture for the whole cohort and stratified by estrogen use status are shown in Table 2. The incidence rates differed between the two menopause groups and between estrogen use strata.

Women who underwent surgical menopause had a lower incidence of hip fracture (13.6 vs 16.5 fractures per 1,000 person-years, p<.05) and a higher incidence of wrist (9.3 vs 7.8 per 1,000, p<.05) and any nonvertebral fracture (54.2 vs 50.3 per 1,000, p<.05), compared to women with natural menopause. When stratified by estrogen use status, the age-adjusted incidence rates of fracture were generally highest among women who had never used estrogen and lowest among current estrogen users. Among women who never used oral estrogen, the age-adjusted incidence rates of hip fracture were lower (14.2 vs 16.4 per 1,000, p<.05), but the rates of wrist (10.3 vs 7.6 per 1,000, p<.05) and any nonvertebral fracture (61.4 vs 48.9 per 1,000, p<.05) were higher for women with surgical menopause, compared to natural menopause. Among current users of estrogen, women with surgical menopause had lower incidence rates of hip, wrist, and any nonvertebral fracture (p<.05). We then evaluated fracture risk in multivariable models (Tables 3, 4, 5).

Among women with no history of oral estrogen use, the risks of hip (HR 0.87, 95% CI 0.63–1.21), wrist (HR 1.08, 95% CI 0.76 to 1.54), and any nonvertebral fracture (HR 1.10, 95% CI 0.92 to 1.31) did not differ in multivariable models, even when adjusted for BMD (Table 3).

Among past users of oral estrogen, risks of hip (HR 0.94, 95% CI 0.63 to 1.41) and wrist fracture (HR 0.78, 95% CI 0.50 to 1.23) did not differ significantly in multivariable models or multivariable models adjusted for BMD (Table 4). There was a lower risk of any nonvertebral fracture for women with surgical menopause that bordered on statistical significance (HR 0.79, 95% CI 0.63 to 0.99), but was not significant when adjusted for BMD (HR 0.81, 95% CI 0.64 to 1.02), although the direction of the hazard ratio was the same.

Among current users of oral estrogen, women with surgical menopause had a lower rate of hip (HR 0.38, 95% CI 0.16 to 0.90) and nonvertebral fracture (HR 0.63, 95% CI 0.43 to 0.92), but not wrist fracture (HR 0.56, 95% CI 0.21 to 1.51) (Table 5). When BMD was added to the models, these relationships were not statistically significant.

Discussion

Contrary to our hypothesis, we did not observe an increased risk of any fracture type for surgical compared to natural menopause even when taking history of estrogen use into consideration. The relative risks for hip and wrist fracture identified in our prospective SOF cohort of nearly 10,000 women mirror those found in the retrospective study of 463 women in Olmstead County, Minnesota, which is the only other longitudinal study to evaluate surgical menopause and fracture risk among elderly women. In that cohort, 463 women (187 with no estrogen exposure) with premenopausal bilateral oophorectomy had no increased risk of hip fracture compared to women in their community, but did have a modest (although not significantly) increased risk of distal forearm fracture (11). In the Olmstead county cohort, a nonsignificant trend to increased risk of fracture with earlier onset (per 10-year decrease in age) of estrogen deficiency was identified. Although, a subanalysis performed among estrogen users found that increasing duration of estrogen therapy was not protective for distal forearm or hip fractures.

Whether or not surgical menopause increases the risk of vertebral (spine) fracture is also an important consideration; however, incident vertebral fractures are more difficult than nonvertebral fractures to identify. In contrast to nonvertebral fractures, only about one-third of vertebral fractures are clinically recognized (12). In SOF, prevalent vertebral fractures were identified using lateral thoracic and lumbar spine x-rays at baseline. Incident vertebral fractures were ascertained at the year-16 visit when follow up radiographs were performed. An incident fracture was defined as >20% and >4 mm decrease in vertebral height at any level (13) when compared to the initial radiograph. Because assessment for incident vertebral fracture required that women survive until the year-16 visit, only a subset of the original cohort underwent a second radiograph. Unadjusted analyses indicate that the cumulative risk of vertebral fracture was lower for women with surgical (27/279, 9.7%) compared to natural menopause (210/1295, 16.2%), ($p<0.006$). Given the small numbers of vertebral fractures, statistical power would be low for a complete analysis stratified by estrogen use status. Nonetheless, these results are consistent with the nonvertebral fracture findings in this cohort.

Patterns of trabecular and cortical bone loss may provide a biological explanation for the lack of increased risk of fracture among women with surgical compared to natural menopause. In young adults, prior to the onset of bone loss, the vertebrae, distal radius, and

femoral neck are comprised predominantly of trabecular bone (14). Data from quantitative computed tomography have shown that trabecular bone loss in women appears to begin in the third decade, well in advance of the onset of estrogen deficiency (14) (15). Although trabecular bone loss appears to accelerate slightly with the menopausal transition, continued loss wanes among elderly women (14) (15). In contrast, cortical bone loss appears to either begin or accelerate in midlife (around the time of menopause), and decline in a linear manner (14).

Studies conducted among older postmenopausal women have shown that femoral and lumbar spine BMD measures (assessed by DXA) do not differ between women with bilateral oophorectomy and intact ovaries (16; 17). Furthermore, a prospective study among older postmenopausal women that carefully controlled for estrogen replacement therapy demonstrated that total hip, femoral neck, and lumbar spine bone loss among women with bilateral oophorectomy or with only hysterectomy was no greater than bone loss among naturally menopausal women (17). Within our study, mean total hip, calcaneal, and distal radius bone mineral density measures were significantly higher for women who underwent surgical compared to natural menopause, likely due to the fact that more women in the surgical menopause group were current users of estrogen. Among women in SOF who had never used oral estrogen, these BMD measures did not differ significantly between the two menopause groups (data not shown). The lack of significant difference in BMD may explain why there was not a higher risk of fracture among women with surgical menopause (compared to natural menopause) and, further, why addition of BMD as a covariate in multivariable models stratified by, and adjusted for, duration of estrogen use did not change the results.

It is possible that recall might affect the ability of women to accurately report their menopausal status or the age at which they underwent hysterectomy, oophorectomy, or menopause. Validation of menopause type was not performed in the SOF cohort because it was shown to be accurately reported in other cohorts (18; 19). In general, self-report of surgery agrees very well with medical records (kappa value > 0.9) (19). In the Rancho Bernardo cohort of women aged 60–89 who had characteristics (mean age 74, primarily white and educated) similar to the SOF cohort, the oophorectomy status of a subsample of women who had undergone hysterectomy was validated against medical records (18). Self-reported bilateral oophorectomy was confirmed by medical records in 96% of cases; validity was less if oophorectomy was not bilateral (18). To minimize misclassification bias in our study, we classified women as surgical menopause only if premenopausal *bilateral* oophorectomy was reported. Moreover, we performed a subanalysis for excluded women with uncertain oophorectomy status, and confirmed these results were similar to those included as surgical menopause (data not shown). These data provide reassurance that random misclassification of ovarian status is an unlikely explanation for the lack of association of menopause type and fracture risk. Fracture outcome misclassification is also unlikely in this study as fracture reports were adjudicated without knowledge of menopause status.

As this is a study of primarily white women, it is not generalizable to women of other races. However, white women have a higher risk of fracture than other races or ethnicities and they account for the greatest amount of health resource utilization related to osteoporotic fracture. Finally, while subgroup analyses may have limited power to detect significant differences, we did find statistical differences in the comparisons among current estrogen users (the group with the smallest sample size and the fewest number of events). Therefore, we don't believe the subgroup analyses are underpowered. Further, it is reassuring that the hazard ratios are <1.0 for all fracture types among both past and current estrogen users, and for hip fracture among never users. If the differences in wrist and any nonvertebral fracture were

statistically significant among never users, then, in clinically meaningful terms, premenopausal bilateral oophorectomy would result in 5 additional nonvertebral fractures per 1000 person-years of observation and less than one additional wrist fractures per 1000 person-years for women with surgical compared to natural menopause.

This study has many strengths. SOF is the first large, prospective, cohort study to evaluate whether surgical menopause increases the risk of nonvertebral fracture. It is also the first study to provide prospectively-assessed, stratified nonvertebral fracture rates for practitioners to use when counseling women at the time of hysterectomy or after natural menopause. In addition, the SOF cohort provides an unparalleled opportunity with the large numbers of women unexposed to oral estrogen therapy after menopause (over 50% of the cohort) to evaluate fracture risk among women without estrogen exposure for over 2 decades since menopause.

Our findings are important to help inform decision making among premenopausal women preparing to undergo hysterectomy. Many studies in the US and Europe have documented changes in attitudes towards estrogen therapy and have demonstrated a decline in hormone therapy use and prescribing since the results of the Women's Health Initiative (WHI) were published (20–22). It is also possible that fewer women in the coming years will choose to use oral estrogen therapy after surgical menopause. Epidemiologic studies suggest that premature menopause (surgical or natural) without estrogen therapy is associated with an increased risk of heart disease and decreased long-term survival (23; 24). Other potential risks to consider at the time of oophorectomy are the potential for decreased libido if the ovaries are removed and risk of repeat surgery for ovarian pathology if the ovaries are retained (25). Moreover, since one of the primary reasons for bilateral oophorectomy is ovarian cancer prophylaxis, patients must weigh the risk of fracture against the risk of ovarian cancer which, over a lifetime for women at average risk, is about 1.4% (26). It is important to note that while there is no accurate screening test for ovarian cancer and the harms of screening for it in average-risk women outweigh the benefits (27), assessment of bone density is predictive of fracture risk in postmenopausal women and, thus, screening for osteoporosis is recommended for all women aged 65 and older (28). Furthermore, there is effective treatment for osteoporosis and for prevention of osteoporotic fracture (29; 30).

Conclusions

This study is the first to prospectively assess the risk of fracture associated with surgical menopause and provides some reassurance that the long-term risk of nonvertebral fracture is not substantially increased for postmenopausal women who experienced surgical menopause, even in the absence of postmenopausal estrogen therapy. Our risk estimates are similar to those reported by a good-quality, retrospective cohort study (11), giving credence to their use in the clinical setting. The lack of increased hip fracture risk among women who underwent surgical menopause (compared to natural) is reassuring given that surgical menopause is common (1) and hip fractures are associated with the greatest morbidity, mortality, and public health burden of any fracture type (31; 32).

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Table 1

Baseline characteristics by menopause type

	Menopause Type		
Characteristics	**Surgical**	**Natural**	**Overall**
	N=1157	**N=5459**	**p**
Demographic Characteristics			
Age at baseline, mean (SD), y	70.8 (4.9)	71.7 (5.4)	<.001
Age at menopause, mean (SD), y	44.3 (7.4)	48.9 (4.9)	<.001
Dietary/Lifestyle Factors			
Calcium supplement intake, mean (SD), mg/week	2942 (4132)	2640 (4243)	.03
Smoking, mean (SD), pack-years	12.5 (21.8)	10.7 (19.9)	.01
Alcohol intake in last month, No. (%), number of drinks			.05
Heavy (>14/week)	46 (4.0)	225 (4.1)	
Light-mod (1–14/week)	562 (48.6)	2857 (52.3)	
None	549 (47.5)	2377 (43.5)	
Medical History			
Number of children breastfed, mean (SD)	1.1 (1.3)	1.3 (1.6)	<.001
Excellent/good self-reported health, No. (%)	931 (80.5)	4646 (85.1)	<.001
Diabetes, No. (%)[b]			.05
Yes, no insulin	77 (6.7)	285 (5.2)	
Yes, uses insulin	17 (1.5)	54 (1.0)	
Medications			
Oral estrogen use, No. (%)			<.001
Current	345 (30.2)	351 (6.5)	
Past	366 (32.0)	1357 (25.2)	
Never	433 (37.9)	3683 (68.3)	
Duration of use, mean (SD), y	7.1 (9.8)	1.8 (4.5)	<.001
Range–overall	*0 – 53.0*	*0 – 40.0*	
Mean (SD), range–past users	*6.4 (7.1) 0 – 43.0*	*4.5 (5.5) 0 – 40.0*	
Means (SD), range–current users	*16.7 (10.4) 0 – 53.0*	*9.6 (8.7) 0 – 40.0*	
Long-acting benzodiazepine use in last 12 months, No. (%)	130 (11.4)	455 (8.4)	.001
Physical measures			
Weight at baseline, mean (SD), kg	67.8 (13.1)	66.7 (12.4)	.01
Depth perception, mean (SD) [+]	2.0 (2.2)	2.3 (2.8)	<.001
Contrast sensitivity, mean (SD) [*]	76.6 (36.5)	73.2 (35.7)	.004
BMD, distal radius (g/cm^2)	0.373 (0.090)	0.356 (0.083)	<.001
BMD, calcaneus (g/cm^2)	0.414 (0.100)	0.398 (0.093)	<.001
BMD, total hip (g/cm^2), visit 2, mean (SD)	0.776 (0.141)	0.746 (0.125)	<.001

Abbreviations: BMD, bone mineral density; SD, standard deviation

[+] Standard deviation of 4 Howard-Dohlman Optical Distance scores

[*] Overall contrast sensitivity score for low spatial frequency (both eyes)

Table 2

Age-adjusted rate of fracture per 1000 person-years of follow-up

	Menopause Type	
Whole Cohort	**Surgical**	**Natural**
Hip	13.6 (13.5–14.4)	16.5 (16.4–17.2)
Wrist	9.3 (9.1–10.0)	7.8 (7.8–8.5)
Any Nonvertebral Fracture	54.2 (53.8–55.1)	50.3 (50.2–51.0)
Never use of estrogen		
Hip	14.2 (14.0–14.9)	16.4 (16.4–17.2)
Wrist	10.3 (10.2–11.0)	7.6 (7.6–8.3)
Any Nonvertebral Fracture	61.4 (61.0–62.3)	48.9 (48.8–49.6)
Past use of estrogen		
Hip	9.4 (9.2–10.1)	17.7 (17.5–18.5)
Wrist	27.7 (26.5–29.2)	11.8 (11.6–12.6)
Any Nonvertebral Fracture	54.8 (53.6–56.3)	75.8 (75.0–76.9)
Current use of estrogen		
Hip	3.7 (3.6–4.4)	14.1 (13.8–14.8)
Wrist	2.3 (2.2–3.0)	5.8 (5.6–6.5)
Any Nonvertebral Fracture	24.5 (24.3–25.3)	43.9 (43.4–44.7)

Table 3

Estimated relative hazard of fracture among never users of oral estrogen

	Menopause Type Hazard Ratio (95% CI)	
	n=4116	
	Surgical	**Natural**
	(n=433)	**(n=3683)**
Hip	(n fx=46)	(n fx=514)
Unadjusted	0.84 (0.62–1.14)	1.00
Multivariable	0.87 (0.63–1.21)	1.00
Multivariable+Calc BMD	0.87 (0.63–1.21)	1.00
Model n=3738		
Wrist	(n fx=44)	(n fx=360)
Unadjusted	1.14 (0.83–1.56)	1.00
Multivariable	1.08 (0.76–1.54)	1.00
Multivariable+Dist BMD	1.10 (0.78–1.57)	1.00
Model n=3703		
Any non-vertebral	(n fx=175)	(n fx=1444)
Unadjusted	1.17 (1.00–1.37)	1.00
Multivariable	1.10 (0.92–1.31)	1.00
Multivariable+Calc BMD	1.11 (0.93–1.32)	1.00
Model n=3461		

Multivariable models adjusted for age, weight, age at menopause, calcium intake (supplement), pack-years smoking, number breastfed, self-reported health status, benzodiazepine use, depth perception, contrast sensitivity

Table 4

Estimated relative hazard of fracture among past users of oral estrogen

	Menopause Type Hazard Ratio (95% CI)	
	n=1723	
Fracture Type	**Surgical**	**Natural**
	(n=366)	**(n=1357)**
Hip	(n fx=37)	(n fx=166)
Unadjusted	0.98 (0.69–1.40)	1.00
Multivariable	0.94 (0.63–1.41)	1.00
Multivariable+Calc BMD	0.95 (0.63–1.42)	1.00
Model n=1566		
Wrist	(n fx=31)	(n fx=136)
Unadjusted	0.94 (0.64–1.39)	1.00
Multivariable	0.78 (0.50–1.23)	1.00
Multivariable+Dist BMD	0.84 (0.53–1.33)	1.00
Model n=1558		
Any non-vertebral	(n fx=116)	(n fx=512)
Unadjusted	0.90 (0.73–1.10)	1.00
Multivariable	0.79 (0.63–0.99)	1.00
Multivariable+Calc BMD	0.81 (0.64–1.02)	1.00
Model n=1438		

Multivariable models adjusted for age, weight, age at menopause, calcium intake (supplement), pack-years smoking, number breastfed, self-reported health status, duration of oral estrogen use, benzodiazepine use, depth perception, contrast sensitivity

Table 5

Estimated relative hazard of fracture among current users of oral estrogen

	Menopause Type Hazard Ratio (95% CI)	
	n=696	
	Surgical	**Natural**
	(n=345)	**(n=351)**
Hip	(n fx=12)	(n fx=21)
Unadjusted	0.44 (0.21–0.89)	1.00
Multivariable	0.38 (0.16–0.90)	1.00
Multivariable+Calc BMD	0.43 (0.18–1.03)	1.00
Model n=637		
Wrist	(n fx=10)	(n fx=14)
Unadjusted	0.59 (0.26–1.34)	1.00
Multivariable	0.56 (0.21–1.51)	1.00
Multivariable+Dist BMD	0.73 (0.27–2.00)	1.00
Model n=630		
Any non-vertebral	(n fx=73)	(n fx=84)
Unadjusted	0.65 (0.48–0.90)	1.00
Multivariable	0.63 (0.43–0.92)	1.00
Multivariable+Calc BMD	0.69 (0.48–1.01)	1.00
Model n=584		

Multivariable models adjusted for age, weight, age at menopause, calcium intake (supplement), pack-years smoking, number breastfed, self-reported health status, duration of oral estrogen use, benzodiazepine use, depth perception, contrast sensitivity