Published in final edited form as:
Menopause. 2011 September ; 18(9): 967–973. doi:10.1097/gme.0b013e31821b8484.

Increased Incident Hip Fractures in Postmenopausal Women with Moderate-to-Severe Pelvic Organ Prolapse

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Abstract

Objective—To examine the association between fracture and pelvic organ prolapse (POP) in postmenopausal women enrolled in the Women's Health Initiative Estrogen plus Progestin (WHI-EP) trial.

Methods—POP was assessed as cystocele, rectocele or uterine prolapse, and was graded as "*absent-to- mild"* or "*moderate-to-severe"*. Cox proportional hazard analyses (adjusting for age, BMI, race, asthma, emphysema, thyroid disease, family history of fracture, regular menses, age at menopause, nulliparity, history of hormone therapy [HT], history of falls, SES, calcium and vitamin D supplementation and physical activity) explored relationships between *moderate-to-severe* POP and incident bone fractures.

Results—*Moderate-to-severe* grade POP was identified in almost 8% of women (n=1,192). Over a follow up duration of 7.41 ± 2.18 years (mean ± SD), 2,156 incident fractures were observed; the most common fracture site was *lower arm* (n=615, 28.51%) followed by *hip* (n=205, 9.51%). Adjusted analyses confirmed *moderate-to*-severe POP (of any type) as an independent risk factor for incident *hip* fractures (HR 1.83, 95% CI 1.16–2.89, p=0.010). On analyses stratified by assigned treatment (HT versus placebo) *moderate-to-severe* rectocele emerged as an independent predictor of incident *spine* (HR 2.61, 95% CI 1.04–6.56, p=0.042) and *lower arm* fractures (HR 1.87, 95% CI 1.06–3.29, p=0.030) in the placebo group.

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This work was presented as an abstract at the annual meeting of the North American Menopause Society, September 2008.

Financial Disclosure: None

Conclusion—We identify *moderate-to-severe* POP (any type) in postmenopausal women as a risk factor for *hip* fracture; *moderate-to-severe* rectocele holds additional risk for *spine* and *lower arm* fractures in women not on HT.

Keywords

Prolapse; Fracture; WHI; Estrogen; Progesterone; Rectocele; Hip

Introduction

Pelvic organ prolapse (POP) is a recognized contributor to morbidity in an aging female population (1–2) and to the overall health care cost in the community. More than 300,000 surgical procedures are reportedly performed annually for POP in the USA, with incurred cost in excess of $1 billion (3–4). The prevalence of POP attests to the magnitude of its potential health care burden. As many as 41% of postmenopausal (PM) women enrolled in the Women's Health Initiative Estrogen Plus Progestin (WHI-EP) Trial demonstrated some degree of POP (2).

Both qualitative and quantitative deficiencies in pelvic collagen are believed to exist in women with POP (5–14). Conversely, a predisposition to POP is identified in women afflicted by generalized connective tissue disorders (15). The role of skeletal collagen in conferring architectural tissue strength is underscored by an increased incidence of fractures in collagen disorders like Marfan and Ehrler Danlos syndromes (16–18). Limited data are suggestive of global collagen deficiency in women with evidence of POP (14, 19–21). Pursuing a hypothesis that PM women with evidence of POP may be at an enhanced lifetime risk for skeletal fragility, we previously identified an association between *moderate-to-severe* POP and compromised skeletal integrity in the PM population (22). Analyses of baseline data from the WHI-EP trial revealed a higher prevalence of low bone mineral density (BMD) and an enhanced likelihood for fractures (after age 55 years) in PM women identified with *moderate-to-severe* POP compared to those with *absent-to-mild* POP (22), thus expanding the spectrum of health concerns associated with POP.

Extending our earlier observations, we herein demonstrate that PM women with *moderate-to-severe* POP are significantly more likely to experience incident fractures compared to those with *absent-to-mild* POP. The current study was undertaken utilizing the longitudinal data on PM women recruited in the WHI-EP Trial, details of which have previously been published (23).

METHODS

Study Population

In the WHI-EP randomized controlled trial, 16, 620 postmenopausal women aged 50 to 79 years with an intact uterus at baseline were recruited at 40 US clinical centers between September 1993 and July 2002; 12 were subsequently excluded due to a change in the hysterectomy status. The participants (16, 608) were randomly assigned to receive conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, (n=8,506) versus placebo (n=8,102).

POP was evaluated at baseline by a standardized pelvic examination(2) and was documented as either *absent* or, if *present*, was categorized into distinct anatomical types, i.e. cystocele, rectocele and uterine prolapse. The severity of POP was graded with reference to the introitus. Three grades of increasing descent of pelvic organs were described: *mild* (descent of the most dependant part of pelvic organs into the vagina but not reaching the introitus),

moderate (descent down to the level of the introitus) and *severe* (descent beyond the introitus). All assessments were performed with the participant in a supine position and performing the Valsalva maneuver (2). *Moderate-to-severe* POP was stated as the exposure variable (independent) for the assessment of a relationship with incident fracture by bone site (dependent).

Independent variables of interest included age, race/ethnicity (White, Black, Asian, Hispanic, Other), gynecologic history including age at menarche (categorized as <9, 9–13, ≥14 years), history of regular periods in premenopausal years (yes/no), age at menopause (years), parity, history of prior use of hormone therapy (HT) (never, <5 years, 5–9 years, ≥10 years), history of use of oral contraceptive (OCP) (ever/never), medical history including any history of thyroid disorders (any type, yes/no), asthma (yes/no), emphysema (yes/no), social history including a history of smoking ≥100 cigarettes ever (yes/no), physical activity (energy expenditure in metabolic equivalents [METS], per week), history of falls in past 12 months (yes/no), family history of bone fractures (broken bone in mother or father, yes/no), and current use of calcium and/or vitamin D supplements. Anthropometric measures included body mass index (BMI) and waist to hip ratio (WHR) both as continuous variables. Parity was available as an ordinal variable (−1 to 9; "−1" referred to "never having been pregnant" and "0" referred to "never had a term pregnancy"). Parity was re-coded as "nulliparous" if there was no history of a prior live birth. Age at menarche ≥14 years was coded as "late menarche" and the age of menopause < 45 years was defined as "early menopause". HT was dichotomized as never/ever. Annual household income, reflecting the socio-economic status (SES), was dichotomized at 50K as previously described (24).

Outcome measures and follow-up

Fracture outcomes were ascertained by a semi-annual questionnaire and included hip, wrist/lower arm, clinical vertebral and total fractures (24). Reported events were verified by local and central adjudication involving review of radiological reports. For the presented analyses, the primary outcome measures were "any fracture" and the site of fracture (hip, spine, and lower arm). The WHI-EP trial was terminated following an average of 5.6 years; in the presented study, participants were followed over 7.41 ± 2.18 years. Follow-up time was calculated from the date of study entry to the date of fracture or date of last exam, whichever came first. Those with missing follow-up data (n=53) and POP status (n=1), and known osteoporosis at baseline (n=794) were excluded for the present analyses; 15, 760 PM women constituted the study sample to explore the hypothesis that *moderate-to-severe* POP is a risk factor for fracture in PM women (Figure 1).

Statistical analysis

Demographic and clinical characteristics were compared between those with *moderate-to-severe* POP and those with *absent-to-mild* POP using two sample t-tests and chi-square tests for continuous and categorical variables, respectively.

Cox proportional hazard models were constructed to evaluate the effect of POP on fracture. The proportional hazards assumption was tested using Schoenfeld residuals and by comparing the plot of the log (–log [survival]) vs. log of survival time; if the graph resulted in parallel lines, the predictor variable was considered "proportional" (25). Adjustment variables included those independent variables that were previously recognized to be associated with the likelihood for fracture at age >55 in our prior analyses utilizing the baseline data for the cohort (22) and included age, race/ethnicity, early menopause, parity (yes, no), hormone use (ever, never), regular periods in premenopausal years (yes/no), BMI (kg/m^2), history of thyroid disorders, history of asthma, history of ever smoking ≥100

cigarettes, history of falls, family history of bone fractures (broken bones in mother or father), SES, METS, current use of calcium and vitamin D supplementation and intervention arm (HT versus placebo). Interaction product terms were created between POP sub-types and intervention arm of the clinical trial (HT or placebo) along with the main effects terms in the fully adjusted models.

Given the known propensity for repeat fracture in those with a history of bone fracture (26), sensitivity analyses were performed after excluding PM women who had previously fractured in their lifetime (ever fracture) to determine the association between *moderate-to-severe* POP with risk of a *first* fracture occurring during period of observation. Continuous data are presented as mean ± standard deviation whereas categorical data are shown as percentage (numbers). Magnitude of risk is presented as hazard ratio (HR) ± 95% confidence interval (95% CI). All statistical tests used two t-tailed α of 0.05 and Stata SE 10.1 for Windows (StataCorp, College Station, TX). Approval from the WHI Publication Committee was obtained prior to accessing the study database.

Results

Moderate-to-severe POP (all types) was identified in 1,192 participants (7.56%); cystocele was the most common anatomic variant (5.32%), followed by rectocele (2.72%) whereas uterine prolapse was noted in 1.20%; additional smaller numbers presented with combinations of the various anatomical (cystocele, rectocele or uterine) variants of *moderate-to-severe* POP. Of the documented incident fractures (n=2,156), the most common site was the *lower arm* (28.51%; n=615) followed by *hip* (9.50%; n=205). Of the hip fractures, the majority were the first fracture sustained during the period of observation (81.95%; n=168).

As shown in Table 1, compared to women with *absent-to-mild* POP, those with *moderate-to- severe* POP were older ($p<0.001$), were significantly less likely to be of Black race, be nulliparous ($p<0.001$), were less likely to smoke ($p<0.001$), to report early menopause ($p=0.007$), or to acknowledge a prior use of OCP ($p=0.040$) or HT ($p<0.001$); those with *moderate-to-severe* POP were significantly more likely to be of Asian ($p<0.001$) race, to report a prior history of fracture ($p=0.003$), to have a higher BMI ($p<0.001$), and to belong to lower SES as reflected by an annual household income <50K ($p=0.016$).

Association between the various anatomic variants of POP and site specific incident fractures is presented in Table 2. Adjusted analyses confirmed *moderate-to severe* POP (any anatomic type, and *moderate-to-severe* rectocele and cystocele) as independent risks for incident *hip* fractures.

A statistically significant interaction was observed between incident lower arm fracture with *moderate-to severe* POP and with *moderate-to-severe* rectocele (p values for interaction = 0.046 and 0.022, respectively) with respect to treatment arm. Stratified analyses by trial assigned intervention (HT versus placebo) identified *moderate-to-severe* rectocele as an independent risk factor for incident lower arm (Figure 2) and spine (Figure 3) fracture in PM women randomized to placebo but not in those receiving HT.

Hazard ratios for site specific incident fractures were further assessed comparing PM women with *moderate-to-severe* POP with those with *absent* POP (i.e. those with *mild* POP were excluded from the reference group), and confirmed stability of the observed associations between *moderate-to-severe* POP and incident hip fracture (data not shown Additional sensitivity analyses excluded those with a history of fracture prior to enrollment in the trial (Table 3). *Moderate-to-severe* POP was again identified as a risk for site specific

incident fracture in PM women not on HT; the highest hazard magnitudes were observed in those with *moderate-to-severe* rectocele.

Given the retrospective cohort study design, a likelihood that the observed differences in incident fractures between the two cohorts (i.e. those with *moderate-to-severe* compared to *absent-to-mild* POP) could have resulted from a differential in the duration of follow up was considered. Interestingly, the mean duration of follow up was statistically significantly shorter in women with *moderate- to- severe* compared to those with *absent-to-mild* POP (7.78 ± 1.47 versus 7.97 ± 1.57 years, $p<0.001$). These findings suggest that the actual magnitude of fracture risk relating to *moderate -to-severe* POP may even be of a greater magnitude than what is observed.

Discussion

In line with our earlier observation (22), our current analyses corroborate our hypothesis relating moderate-to-severe POP in postmenopausal women with skeletal fragility. Our analyses of the longitudinal data available on women enrolled in the WHI-EP trial identify *moderate-to-severe* rectocele as an independent risk for postmenopausal hip fracture. The skeletal site specific predilection to fracture however is likely a reflection of power related constraints, as an enhanced risk for lower arm and spine fractures was also observed in postmenopausal women with *moderate- to- severe* POP who were assigned to the placebo arm of the clinical trial. These latter observations imply protective effects of menopausal HT on reducing incident fractures in PM women with *moderate-to-severe* POP.

We previously described an association between *moderate-to-severe* POP and likelihood of fracture in aging postmenopausal women (>60 years) (22). Our current and prior observations have been corroborated by Melton et al (27) who, in a retrospective cohort study of 9, 258 women followed for a median of 13.6 years following hysterectomy, described an association between prior surgery for uterine prolapse and fracture risk.

The consistency of the observed relationships between individual anatomical variants of *moderate-to-severe* POP with incident fractures by site on adjusted analyses as well as on sensitivity analyses add credence to our hypothesis that POP be regarded as a focal manifestation of generalized tissue compromise. A site specific differential in pelvic connective tissue composition and relationship thereof with the skeletal matrix is suggested by our analyses. Qualitative and possibly quantitative distinctions in the pelvic fascia from anatomically distinct compartments are thus implied, albeit remain far from understood. Intra-individual and inter-individual variations in pelvic fascia are well appreciated and this tissue heterogeneity underlies the lack of consensus regarding embryological origins of the pelvic fascia (28); histological distinctions in the fascia of the pelvic compartments are similarly poorly understood. While the underlying mechanisms unifying the consistently observed relationships between rectocele and bone fracture remain unclear, these observations underscore a need for appropriately designed studies focusing on site specific differences in tissue composition within the pelvic compartments.

A role for the loss of ovarian hormones in the pathogenesis of POP remains far from clear. An increased risk for POP is described in association with polymorphism in ERα as well as with ERβ (29–30) implying a role for estrogen signaling (or lack of effects thereof) in the pathogenesis of POP. The picture is, however, clouded by inconsistencies in the data relating the presence and progression of POP to the use of menopausal HT or selective estrogen receptor modulators (31–34). Worsening POP was reported in the PM women randomized to the EP arm of the WHI-EP trial (31). A similar lack of efficacy against POP was observed with the use of selective estrogen receptor modulators raloxifene and

tamoxifen and conjugated equine estrogen by healthy postmenopausal women (32); following 20 weeks of intervention, progression in POP was observed in 75% of the patients randomized to raloxifene, 60% who received tamoxifen and 22% of the patients receiving conjugated equine estrogen (32). Primary damage to the connective tissue of the pelvic floor occurs during pregnancy and childbirth, and a role for the loss of ovarian hormones concomitant with menopause in the pathogenesis of, or progression in, POP thus remains far from clear.

Based on the current evidence, the role for HT in women with POP is limited to treatment of symptoms relating to vaginal atrophy. Our data suggest beneficial influences of menopausal HT in reducing fracture risk in PM women with *moderate-to-severe* POP. While these findings reiterate the well recognized protective effects of HT on fracture risk (24), future studies however are needed to help establish a preventive role for postmenopausal HT in mitigating fracture risk in women with *moderate-to-severe* POP.

Although we herein hypothesize that compromised tissue collagen may be a mechanism that unifies POP (reflective of a weakened pelvic floor) and skeletal fragility, our data cannot elucidate the underlying pathophysiological mechanisms. The relatively subjective nature of the evaluations as well as the supine positioning of the participants at the time of POP grading (33–34) are limitations intrinsic to the study design that may have compromised sensitivity in detecting lesser grades of POP. We attempted to redress this latter concern by targeting obvious descent of pelvic organs as our variable of interest (22), thus confining our definitions to more severe degrees of POP. In the subset of women who underwent bone mineral density (BMD) assessment at baseline, our prior analyses (22) identified significantly lower total body BMD in those with *moderate-to-severe* POP. While the paucity of incident fracture events in the limited cohort who did undergo BMD testing (BMD was evaluated in only a subset, n=1,024; 46 of 958 with *moderate-to-severe POP* and 634 of 10,101 with *absent-to-mild* POP underwent BMD evaluation) limits us from commenting on the contributions of deteriorating BMD to fracture risk, we attempted to address this deficiency by excluding those with a known history of osteoporosis as well as those with prior history of fracture. Although the direction and the magnitude of HR's for the observed associations between individual anatomical variants of *moderate-to-severe* POP and fracture site were maintained on sensitivity analyses, the resulting model instability (widening of CI's) and loss of statistical significance to some of the associations likely reflect power constraints.

Conclusion

Our analyses of longitudinal data for the WHI-EP cohort identify *moderate-to-severe* POP, a prevalent gynecological entity, as an independent risk factor for incident fracture in postmenopausal women. We reaffirm the previously observed relationships (22) between *moderate-to-severe* POP in general, and *moderate-to-severe* rectocele, in particular, with skeletal fragility. Considering the prevalence of POP in PM women (almost 8% of PM women enrolled in WHI-EP Trial demonstrated *moderate-to-severe* POP) and the observed association with incident hip fractures (which have the highest morbidity and mortality), our findings hold public health implications (35). While our analyses suggest that HT was protective against incident fracture in PM women with *moderate-to-severe* POP, these findings must be interpreted with caution given the retrospective nature of our analyses, our inability to comment on the occurrence of "non informative" events given the limitations intrinsic to working with an existing dataset, and the wide confidence intervals that are likely reflective of power constraints. It should be noted that comparable efficacy data for commonly used antiresorptive treatments other than HT (e.g. bisphosphonates, SERM's, calcitonin or parathyroid hormone) have not been specifically substantiated in this

population of postmenopausal women identified at risk for fracture. Our findings suggest that considerations on the choice of fracture prevention therapy in postmenopausal women should incorporate the status of pelvic organ descent.

Acknowledgments

Funding/Support: The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, US Department of Health and Human Services.

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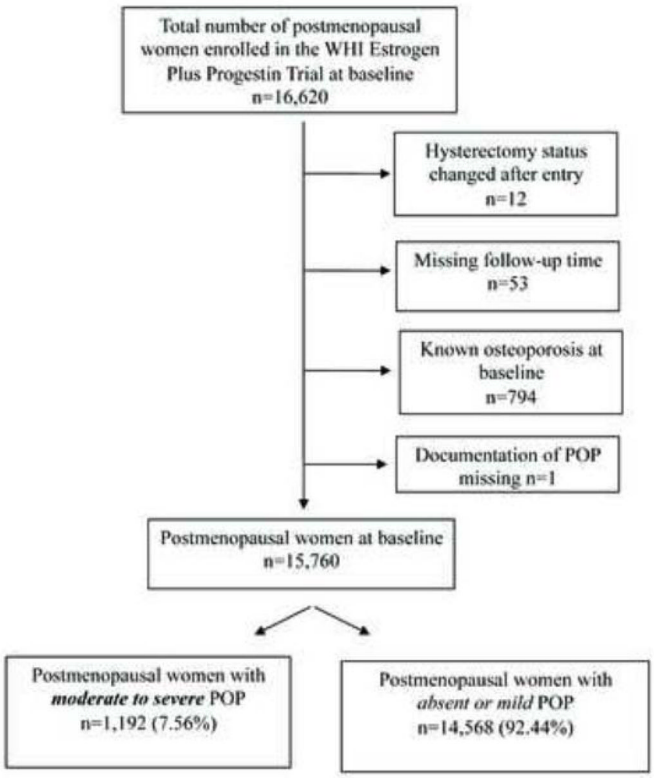

FIG. 1.

Flowchart of study participants in the WHI Estrogen Plus Progestin clinical trial. WHI, Women's Health Initiative; POP, pelvic organ prolapse.

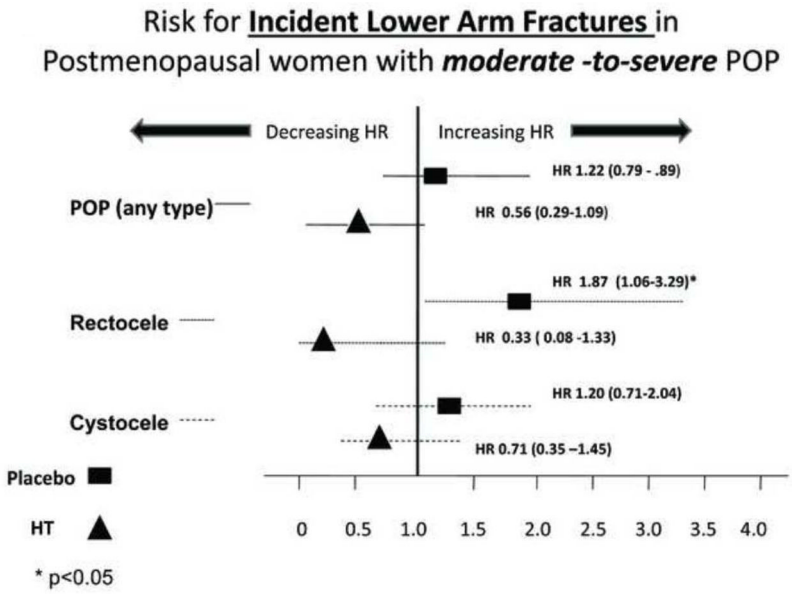

FIG. 2.

Risk of incident lower arm fracture in postmenopausal women with moderate to severe compared with those with absent to mild POP. POP, pelvic organ prolapse; HR, hazard ratios; HT, hormone therapy.

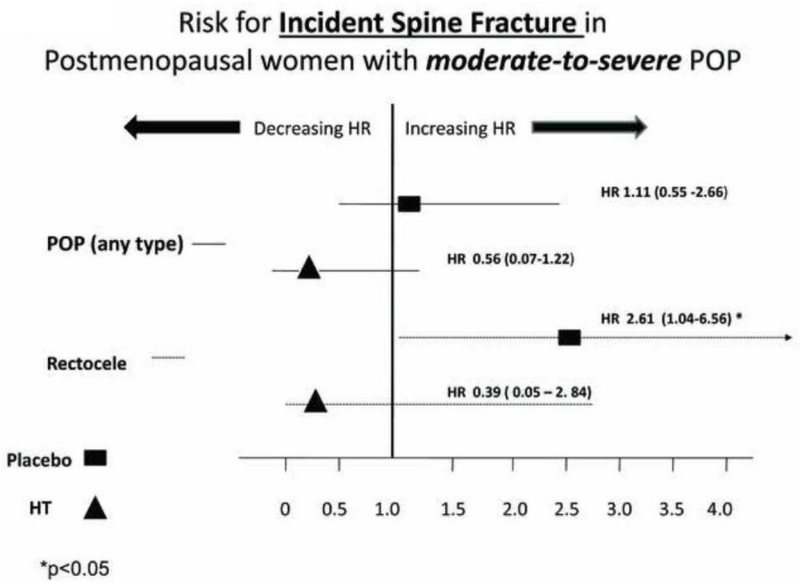

FIG. 3.

Risk of incident spine fracture in postmenopausal women with moderate to severe compared with those with absent to mild POP. POP, pelvic organ prolapse; HR, hazard ratios; HT, hormone therapy.

Table 1

Characteristics of the cohort by severity of pelvic organ prolapse (POP).

Variable	*Moderate-to-Severe* POP 7.56% (1,192)	*Absent-to-Minimal* POP 92.44% (14,568)	Total n=15,760	P value
Age at study entry	64.76 ± 6.74	62.92 ± 7.09	63.06 ± 7.08	<0.001
Race				
White	82.21 (980)	84.31 (12,250)	84.15 (13,230)	0.056
Black	4.45 (53)	7.12 (1,034)	6.91 (1,087)	<0.001
Asian	5.20 (62)	1.94 (282)	2.19 (344)	<0.001
Hispanic	6.29 (825)	5.16 (750)	5.25 (825)	0.093
History of late menarche [a]	9.66 (115)	10.86 (1,576)	10.77 (1,691)	0.201
History of regular menses	84.36 (1,003)	83.93 (12,144)	83.96 (13,147)	0.697
Nulliparous [b]	1.94 (23)	10.77 (1,562)	10.10 (1,585)	<0.001
Age at menopause (years)	50.10 ± 4.36	49.48 ± 4.38	49.52 ± 4.38	<0.001
Early menopause [c]	14.99 (155)	18.34 (2,283)	18.09 (2,438)	0.007
History of smoking [d]	42.22 (499)	51.13 (7,397)	50.46 (7,896)	<0.001
History of previous fracture	15.66 (174)	12.60 (1,674)	12.83 (1,848)	0.003
History of thyroid disease	20.86 (247)	19.64 (2,841)	19.73 (3,088)	0.309
History of emphysema	2.99 (33)	3.02 (397)	3.02 (430)	0.957
History of asthma	7.33 (86)	6.25 (896)	6.33 (982)	0.146
History of OCP [e] use (ever)	40.86 (487)	43.93 (6,400)	43.70 (6,887)	0.040
History of HT [f] use (ever)	13.59 (162)	17.90 (2,608)	17.58 (2,770)	<0.001
History of falls [g]	34.34 (388)	32.72 (4,437)	32.84 (4,825)	0.266
History of family fracture [h]	42.37 (509)	43.62 (6,354)	43.52 (6,859)	0.403
Annual income <$50,000	71.86 (812)	68.40 (9,429)	68.66 (10,241)	0.016
BMI (kg/m$^{2)}$	29.73 ± 5.65	28.44 ± 5.88	28.53 ± 5.87	<0.001
Waist-to-Hip Ratio	.84 ± .08	.82 ± .08	.82 ± .08	<0.001
Calcium supplementation [i]	49.50 (590)	48.26 (7,030)	48.35 (7,620)	0.411
Vitamin D supplementation [j]	43.20 (515)	42.52 (6,194)	42.57 (6,709)	0.646
METS/week [k]	10.66 ± 12.58	11.60 ± 13.67	11.53 ±13.59	0.025

Data are presented as mean ± standard deviation (continuous) or % (n) (categorical). P-values are calculated by Student's t-tests for continuous variables and chi-square test for categorical variables.

[a] Late menarche is defined as ≥ 14 years of age.

[b] Nulliparous is defined as no prior history of live birth.

[c] Early menopause is defined as menopause at age ≤45 years

[d] History of smoking defined as ≥100 cigarettes ever.

[e] History of use of oral contraceptives (ever)

[f] History of use of hormone therapy (ever)

[g] History of falls defined as falls within the past 12 months.

[h] Family history of fracture defined as fracture in either or both parents after the age of 40 years.

[i] Calcium and vitamin D supplementation defined as any vs. none.

[j] Metabolic equivalents

Table 2

Proportional hazard models demonstrating hazard ratios (HR) and 95% confidence interval (CI) for skeletal site specific fractures sustained during the period of observation in postmenopausal women with *moderate- to- severe* pelvic organ prolapse (POP) compared to those with *absent to minimal* POP.

Outcome	POP[t]	Unadjusted HR (95% CI)	P	Adjusted[*] HR (95% CI)	P
All Fractures (2,156)					
	Any POP	1.00 (0.85, 1.18)	0.997	1.02 (.85, 1.23)	0.811
	Rectocele	1.18 (0.92, 1.51)	0.176	1.19 (.91, 1.56)	0.199
	Cystocele	0.86 (0.55, 1.33)	0.494	1.02 (0.82, 1.26)	0.891
	Uterine	1.00 (0.82, 1.21)	0.965	0.97 (0.60, 1.56)	0.886
Hip (n=205)					
	Any POP	1.85 (1.22, 2.80)	0.003	1.83 (1.16, 2.89)	0.010
	Rectocele	2.12 (1.15, 3.88)	0.016	2.18 (1.14, 4.17)	0.018
	Cystocele	1.81 (0.67, 4.88)	0.239	1.79 (1.05, 3.07)	0.034
	Uterine	1.79 (1.10, 2.91)	0.018	0.95 (0.23, 3.85)	0.941
Spine (n=193)					
	Any POP	0.84 (0.47, 1.50)	0.550	0.76 (0.39, 1.50)	0.435
	Rectocele	1.39 (0.65, 2.96)	0.392	1.42 (0.62, 3.23)	0.407
	Cystocele	1.44 (0.46, 4.50)	0.534	0.48 (0.18, 1.31)	0.151
	Uterine	0.59 (0.26, 1.33)	0.205	1.25 (0.31, 5.06)	0.758
Lower Arm (n=615)					
	Any POP[†]	0.87 (0.63, 1.20)	0.397	0.93 (0.65, 1.34)	0.701
	Rectocele[†]	1.18 (0.75, 1.86)	0.481	1.17 (0.70, 1.97)	0.551
	Cystocele	0.60 (0.22, 1.61)	0.313	0.98 (0.64, 1.49);	0.923
	Uterine	0.91 (0.62, 1.31)	0.607	0.59 (0.19, 1.83);	0.361

[*] Multivariable analyses adjusted for age, BMI, race, asthma, emphysema, thyroid, family history of fracture, regular menses, age at menopause, nulliparity, hormone use, history of falls, income, calcium supplementation, METs per week, and clinical trial intervention arm (HT versus placebo).

[t] Reference group is *absent to minimal* POP

[†] Denotes a statistically significant interaction between anatomical type of *moderate- to- severe* POP and HT (p=0.046 and p=0.022 for interaction between *moderate to severe* POP, any type, and *moderate-to- severe* Rectocele with HT respectively).

Table 3

Proportional hazard models demonstrating adjusted hazard ratios (AHR) for the "first fracture event" sustained during the period of observation in postmenopausal women with *moderate to severe* pelvic organ prolapse (POP) compared to those with *absent to minimal* (referent group) POP (n*ote, those with a "history of fracture" prior to enrollment were excluded from these sensitivity analyses).*

Outcome	Overall [a] AHR (95% CI)	Placebo [b] AHR (95% CI)	HT [c] AHR (95% CI)
Any POP †			
Hip fracture	2.04 (0.99–4.20)	3.09 (1.24– 7.67) ‡	1.12 (0.33–3.82)
Spine fracture	0.83 (0.30–2.30)	1.11 (0.33–3.69)	0.43 (0.06–3.20)
Lower Arm fracture	1.12 (0.68–1.85)	1.64 (0.91–2.94)	0.54 (0.20–1.47)
Rectocele†			
Hip fracture	1.73 (0.54–5.60)	5.28 (1.55–17.98) ‡	§
Spine fracture	2.69 (0.97–7.52)	3.80 (1.13– 12.73) ‡	1.20 (0.16–8.98)
Lower Arm fracture	1.53 (0.75–3.12)	3.34 (1.61 –6.97) ‡	§
Cystocele†			
Hip fracture	2.65 (1.24–5.66) ‡	3.94 (1.48–10.53) ‡	1.67 (0.48–5.74)
Spine fracture	0.57 (0.14–2.35)	1.07 (0.25–4.55)	§
Lower Arm fracture	1.14 (0.64–2.05)	1.47 (0.71–3.03)	0.76 (0.28–2.09)

*AHR (95% confidence intervals) are reported for:

[a]overall population,

[b]enrollees in placebo arm,

[c]enrollees in HT arm of the clinical trial.

Models are adjusted for age, BMI, race, asthma, emphysema, thyroid, family history of fracture, regular menses, age at menopause, nulliparity, hormone use, history of falls, income, calcium supplementation and METs per week and for HT intervention arm (a)

†*Moderate-to-severe* grade of POP compared to reference (*absent to minimal* POP)

‡Statistically significant p<0.05

§No fractures in this group