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Bone Mineral Density Changes Among Women Initiating Proton Pump Inhibitors or H2 Receptor Antagonists: A SWAN Cohort Study

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Abstract

Proton pump inhibitors (PPIs) have been associated with diminished bone mineral density (BMD) and an increased risk of fracture; however, prior studies have not yielded consistent results, and many have suboptimal ascertainment of both PPI use and BMD. We used data from the Study of Women's Health Across the Nation (SWAN), a multicenter, multi-ethnic, community-based longitudinal cohort study of women across the menopause transition to examine the association between annualized BMD changes and new use of PPIs. We compared changes in BMD in new PPI users with changes in BMD in new users of histamine 2 receptor antagonists (H2RAs) and with changes in BMD in subjects who did not use either class of medications. Mixed linear regression models included recognized risk factors for osteoporosis, including demographics, menopausal transition stage, body mass index (BMI), lifestyle factors, as well as comorbidities and concomitant medications. To provide further evidence for the validity of our analytic approach, we also examined the effects of hormone-replacement therapy (HT), a class of medications that should reduce bone loss, on changes in BMD as an internal positive control group. We identified 207 new users of PPIs, 185 new users of H2RAs, and 1,676 non-users. Study subjects had a mean age of 50 years and were followed for a median of 9.9 years. Adjusted models found no difference in the annualized BMD change at the lumbar spine, femoral neck, or total hip in PPI users compared with H2RA users or non-users. These results were robust to sensitivity

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All other authors state that they have no conflicts of interest.

analyses. BMD increased as expected in HT users, supporting the validity of our study design. These longitudinal analyses plus similar prior studies argue against an association between PPI use and BMD loss.

Keywords

BONE MINERAL DENSITY; PROTON PUMP INHIBITORS; HORMONE-REPLACEMENT THERAPY; HISTAMINE 2 RECEPTOR ANTAGONISTS

The musculoskeletal system is metabolically active and responsive to many stimuli, including hormonal and immunologic inputs.^(1,2) The responsiveness of the skeleton has facilitated development of drugs that enhance bone mineral density (BMD) and reduce the risk of fractures.^(3,4) However, it has been increasingly recognized that many commonly used medications may have deleterious effects on the skeleton. Proton pump inhibitors (PPIs) represent one such category of medication suspected of having a negative impact on the skeleton and possibly increasing the risk of osteoporosis and fractures.

There have been at least four published longitudinal epidemiologic studies examining the effects of PPIs on BMD (Table 1).^(5–8) Although several studies have found baseline differences in BMD between PPI users and non-users, none has found consistent associations at most anatomic sites in longitudinal analyses. Moreover, these studies have important methodologic limitations that may hinder interpretation of their findings. First, assessment of PPI use was infrequent—once every 3 to 5 years—as was the testing of BMD. Second, three of the four studies compared PPI use with non-use, without adjusting for potential confounding. Although one study did adjust for gastrointestinal diagnoses, none used other acid-suppressive treatments, such as H2 receptor antagonists (H2RAs), as an alternative control group. Moreover, none employed a new user design, whereby a true BMD baseline (pre-PPI) can be established; this design is thought to be optimal for drug epidemiology.⁽⁹⁾

Because multiple studies have reported that fracture risk is increased in current users of PPIs, many patients are concerned that they may increase their risk of developing osteoporosis if they use PPIs.^(10–12) A clear answer about whether PPIs cause reductions in BMD, possibly putting some users at risk of fracture, would have major public health implications. PPIs are among the most widely utilized medications in the United States, often with ambiguous indications and questionable evidence of efficacy.⁽¹³⁾ Because efficacy may be unclear in many PPI users, it is particularly important to determine whether these agents are safe. If PPIs predispose patients to osteoporosis without clear evidence of benefits, changes in their indications and availability would be indicated.

To address limitations presented by prior work, we compared longitudinal BMD changes in women who initiated PPI use with BMD changes in women who initiated use of H2RAs and with BMD changes in women who did not use either class of medications. This study was conducted among women participating in the Study of Women's Health Across the Nation (SWAN), a large multi-ethnic, community-based, longitudinal cohort of women transitioning through the menopause. To provide additional evidence for the validity of our

study design, we performed similar analyses in women taking hormone-replacement therapy (HT), a class of drugs known to increase BMD and thus who could serve as a “positive control” group.

Materials and Methods

Study design

The Study of Women Across the Nation (SWAN) is a community-based, multi-ethnic longitudinal observational cohort study of the menopause transition that enrolled 3302 pre- or early perimenopausal women between the ages of 42 and 52 years at seven clinical sites across the United States. After enrollment between 1996 to 1998, women are seen annually to monitor a wide variety of measures, with 5 of the 7 sites measuring BMD annually. Information on medication use is collected prospectively at all sites. A detailed description of the study design has been published previously.⁽¹⁴⁾

The primary question of the current study was whether use of PPIs accelerates the rate of bone loss in midlife women. To address this question, we compared the annualized rate of change in BMD among subjects in SWAN who initiated PPIs with the rates of change in BMD in users of H2RAs and in women who did not report use of either class of medications. The annualized change in BMD was calculated as the annual percent change in a linear regression model, facilitating comparison of results across study groups. The change was calculated from a baseline BMD value determined at the visit before the first use of a PPI or H2RA. For participants not reporting use of these medications, we randomly selected a frequency-matched visit to establish a comparable baseline. To provide additional evidence supporting the validity of our study methods, we employed the same methods to test whether HT initiation was associated with a reduction in rates of bone loss (a positive control exposure).

Study sample

We constructed two samples, one to examine the associations between PPI or H2RA use and bone loss (cohort 1, Fig. 1) and the second to examine the relation between HT use and bone loss (cohort 2). To construct cohort 1, we first identified new users of a PPI or H2RA by excluding participants who reported use of either type of medication at the first SWAN visit. Participants who reported PPI or H2RA use at a subsequent visit were identified as new users. Additionally, subjects were required to have undergone at least two BMD measurements after the study baseline (see the section above for definition of baseline for drug users and non-users). We censored subjects reporting use of both a PPI and H2RA at the same visit. New users who discontinued use of these medications were censored at the last annual visit when usage of the drug was reported; they were also censored when a woman using a PPI added an H2RA or vice versa. Women who became pregnant were also censored at the visit before reporting pregnancy. Cohort 2 was created in an analogous fashion.

Written informed consent was obtained from all study participants. The informed consent procedures, study protocol, and forms were approved by all SWAN site Institutional Review Boards.

Assessment of medication use

At each visit, interviewers administered questionnaires to ascertain all medication use since the last study visit, and use was verified by inspection of medication containers. Type of medication was classified from product brand or generic names using a computerized medication dictionary (Iowa Drug Information Service [IDIS] Drug Vocabulary, College of Pharmacy, University of Iowa, Iowa City, IA, USA). PPI and H2RA use was assessed at each visit to determine ongoing use. Dosage of PPIs and H2RAs was not available in the study data set.

Measurement of bone mineral density

BMD of the lumbar spine, femoral neck, and total hip (g/cm^2) was measured by dual-energy X-ray absorptiometry (DXA) using Hologic instruments (Hologic Inc., Waltham, MA, USA). Three sites used Hologic 4500A models throughout, and two sites upgraded from the 2000 to 4500A models during follow-up but cross-calibrated the machines. Each DXA laboratory measured a Hologic anthropomorphic spine phantom daily, and a phantom was circulated among laboratories for cross-calibration. Phantom measurements were analyzed by Synarc, Inc. (Waltham, MA, USA) and calibration regression coefficients used by the study's coordinating center to adjust DXA measurements for minor temporal or geographic variations in densitometer performance. Additional quality-control measures included review of every scan image by a local site investigator and central review of a random subset of 5% of all scans and all problem scans by Synarc, Inc.^(14,15) Short-term in vivo measurement variability was $0.014 \text{ g}/\text{cm}^2$ (1.4%) for the lumbar spine and $0.016 \text{ g}/\text{cm}^2$ (2.2%) for the femoral neck.

BMD measurements were available through the 10th annual SWAN visit for this study.

Osteoporosis risk factors (covariates)

We considered several variables at the baseline visit as potential confounders and included them in adjusted analyses. SWAN participants underwent measurement of height and weight for calculation of body mass index (BMI, weight in kilograms divided by the square of height in meters). They completed interviewer-administered or self-administered questionnaires that assessed demographic characteristics (age, race, ethnicity, income, marital status, education), lifestyle factors (tobacco use, alcohol intake), self-assessed health status, social support (4 items from the 20-item Medical Outcomes Study Social Support Survey),⁽¹⁶⁾ vasomotor symptoms, medication use (bisphosphonates, hormone-replacement therapy, oral glucocorticoids, and thiazide diuretics), and self-reported comorbid conditions (osteoporosis, thyroid disease, any cancer, diabetes mellitus). In addition, physical activity was measured using a modified version of the Baecke Physical Activity Questionnaire (range 3 to 15),^(17,18) but it was not measured at every visit. Menopause transition stage was assessed in SWAN based on bleeding criteria. Categories were: premenopause (no decreased regularity in menstrual bleeding during the last year), early perimenopause

(decreased menstrual regularity in the past year and menstrual bleeding in the past 3 months), late perimenopause (no menses for 3 to 11 months), and postmenopause (no menses for 12 or more months). Women reporting hysterectomy or oophorectomy were classified as surgically menopausal. Menopause transition stage was updated at every study visit.

Follow-up measurements were introduced for time-varying covariates, including menopausal transition stage, vasomotor symptoms, cancer, diabetes mellitus, and the use of bone active agents.

Statistical analysis

We described the baseline subject characteristics in each of the exposure groups using descriptive statistics (mean, median, and range). Continuous variables were analyzed using ANOVA and Kruskal-Wallis tests, whereas categorical variables were analyzed using chi-square tests. Variables were transformed where necessary. The relationship between medication use and annual change in BMD (change between two subsequent annual BMD measurements) was analyzed using a mixed-effects regression modeling strategy, allowing for a random intercept and slope.⁽¹⁹⁾ Factors selected a priori for inclusion in the primary models included years from medication initiation as a continuous linear covariate and several baseline covariates known to be possible correlates of BMD: study site, race/ethnicity (white, African-American, Chinese, Japanese), BMI, age, and menopause transition stage (time-varying).

We also tested covariates of interest (all those listed in Table 2) in sensitivity analyses. Only those covariates with p values < 0.10 in the unadjusted mixed model were entered into the models with the a priori variables from the primary models. Final adjusted sensitivity analysis models included only those covariates with p values < 0.05 in the multivariable mixed-effects regression models. Variables included in these sensitivity analyses differed by anatomic site of BMD outcome (spine: primary model covariates+smoking, diabetes, cancer, osteoporosis, vasomotor symptoms, hormone-replacement therapy, bisphosphonates, thiazide diuretic use, race * PPI use; femoral neck: primary model covariates+income, educational level, physical activity, cancer, diabetes, hormone-replacement therapy, bisphosphonates, thiazide diuretic use; total hip: primary model covariates+educational level, physical activity, cancer, diabetes, hormone-replacement therapy, bisphosphonates, thiazide diuretic use).

We examined for differential BMD effects between PPI and H2RA use and menopausal transition stage by introducing interaction terms (between drug and menopausal status) in the multivariable mixed-effects regression models. Because of marginal significance of interaction terms, we performed a secondary analysis focusing on the period of stable BMD; thus, the analysis examined women's BMD up until 1 year before the final menstrual period. In other secondary analyses, subjects were censored when they reported on the medication questionnaire use of HT, steroids, bisphosphonates, or thiazide diuretics. Two-tailed p values < 0.05 were considered statistically significant for main and interaction effects.

Positive control analyses were conducted in a parallel fashion as the primary analyses. In brief, the positive control exposure of interest was new use of HT compared with non-users (secondary cohort). Baseline for users of HT was chosen as the visit before the start of HT. Non-user baseline visits were frequency matched with the HT users. The BMD outcome was annualized change measured at the lumbar spine, femoral neck, and total hip. Covariates and regression model construction matched the primary analysis.

SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) was used for the analyses.

Results

The baseline characteristics of the three exposure groups in cohort 1 (PPI users, H2RA users, and non-users of PPIs or H2RAs) are shown in Table 2. Women from the three exposure groups were similar in age at cohort entry and were followed for a median of 9.9 years. About half were white in each group with similar distributions of other race/ethnicities represented. The menopausal transition state was different across the three exposure groups with more women in the PPI group being perimenopausal or postmenopausal at cohort entry. The mean BMI in the PPI and H2RA groups were similar but higher than the non-user group. Comorbidities and comedications of interest were more commonly noted in the PPI and H2RA groups. The BMDs at baseline for the three exposure groups were similar across the three anatomic sites. The PPIs used are described in Supplemental Table S1.

The annualized change in BMD for each group was compared in adjusted linear mixed models. The results of the primary models are illustrated in Fig. 2. No differences between exposure groups were observed at any of the anatomic sites. The estimated adjusted changes in BMD by exposure group are shown in Table 3, as are adjusted sensitivity analyses. The sensitivity analysis models did not change the estimated annual changes in BMD in any of the exposure groups.

To examine whether slight imbalances in menopausal status may have confounded the relationship between PPI and H2RA use and BMD, interaction terms were tested. The interaction terms assess the possibility that the effect of medication class on BMD may vary by menopause status. Because one of the interaction terms was borderline significant, we performed an additional analysis censoring subjects 1 year before their final menstrual period, a stage where BMD is generally quite stable.⁽¹⁵⁾ Consistent with the main analysis, neither PPI nor H2RA use was associated with greater loss in BMD compared with non-users in the period from the baseline visit until 1 year before the final menstrual period.

Finally, we examined the HT users, cohort 2, as a positive control exposure. New users of HT ($n = 606$) differed in many baseline characteristics from non-users ($n = 1491$) (Supplemental Table S2). We compared annualized change in BMD across these two groups using the same main model as for the primary analysis. As expected, the annualized rate of BMD decline was significantly lower in the HT users than in the non-user group at all three anatomic sites (Fig. 3).

Discussion

In this study, we failed to find evidence of accelerated bone loss from the hip or spine in midlife women who initiated use of PPIs. Rates of bone loss in the PPI users were similar to rates of bone loss in women who initiated use of H2RA blockers and women who did not use these classes of medications. Rates of bone loss were attenuated as expected in women who initiated use of HT, a finding that provides supportive evidence that our analyses did not generate spurious results.

Previously published studies examining rates of bone loss and/or the risk of fracture in people who use PPIs have generated mixed results, with some studies suggesting significant associations and others not. For example, several cross-sectional analyses have reported a relationship between PPI use and reduced BMD, and a meta-analysis reported a significant association between PPI use and fractures.^(10–12,20,21) In contrast, most prior longitudinal studies have failed to find a significant association between PPIs and BMD,^(5–8) as in our current study. Interpretation of prior studies is compromised, however, by a number of methodological limitations. First, none employed a new-user design in which only subjects initiating drug would be included. This is a preferred method in drug epidemiology and limits the risks of time-varying associations between drug and outcome.⁽⁹⁾ Second, most prior studies assessed drug use and BMD relatively infrequently; some only assessed BMD and PPI use at 5-year intervals. A drug-association study needs frequent assessments of drug exposure, especially in the instance of a PPI that may be used on an as-needed basis. Third, most prior analyses compare users to non-users, without respect to potential confounding.⁽²²⁾ If there is no accurate assessment of symptoms that trigger a treatment (ie, gastrointestinal symptoms and PPI use), then it is always preferred to use an active comparator with similar indications (ie, H2RA). Finally, unlike prior studies, this analysis also included a positive control (HT), providing important supporting evidence that our study design yields valid results.⁽²³⁾

Our study has potential limitations. As an observational study, this study could suffer from potential misclassification of exposure, ie, subjects who mistakenly reported use or nonuse of PPIs. Subjects did bring in medication containers, which should limit misclassification errors. It is also possible that some participants who had used PPIs before SWAN were misclassified as “new users.” It is also possible that some PPI and H2RA users were only taking the medication intermittently, thereby diminishing the intensity of the exposure and reducing any potential harm of these medications on BMD. However, the medication questionnaire in SWAN asks for drugs taken at least twice per week. Unmeasured confounding bias is possible; that is where the use of PPIs is associated with another variable that may affect BMD. We included a robust set of covariates to limit this possibility. Even including other bone-active agents, such as HT and bisphosphonates, did not alter the results (results not shown). We did not assess the association between PPI use and fractures. It is possible that these agents may be associated with fractures independent of any effect on BMD. For example, PPIs could increase the risk of falls, though a recent study found no relationship between PPI use and falls.⁽²⁴⁾ This study only included women going through the menopause transition. Although this is a very important population to study, these results may not generalize to other cohorts. Moreover, because bone loss during the

menopause transition is so rapid,⁽²⁵⁾ it is possible that a small effect of PPIs on rates of bone loss may have been obscured by the rapid bone loss during the menopause transition. However, when the analysis was restricted to premenopausal women, in whom the rate of endogenous bone loss is negligible, we also failed to find evidence of accelerated bone loss in PPI users.⁽¹⁵⁾

In conclusion, we failed to find a significant association between PPI use and BMD loss in women participating in SWAN, a large, multi-ethnic, longitudinal study of midlife women as they transition across the menopause. These findings may have important clinical and methodologic implications. Clinically, the findings add to the body of evidence that PPIs do not affect bone adversely. Although PPIs are likely overused and may present other toxicities, the concern regarding an association with osteoporosis, including the appropriateness of the FDA-required label on PPIs warning consumers about a risk for bone loss, should be reassessed. Methodologically, this study highlights several important approaches that reduce the change of reporting spurious associations. Several of these issues may also impact observational studies assessing the relationship between PPI use and fracture risk. It is important for fracture studies also to pay careful attention to new user designs with active comparators and frequent reassessment of drug use. As future work examines the potential positive and negative effects of medications on bone health, use of techniques employed in this study—a new-user design, improved and more frequent ascertainment of medication use, active measures to address confounding, and the use of a positive control—will be important to improve the consistency and validity of results.

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Authors' roles: DHS developed the analysis plan, interpreted analyses, drafted the manuscript, and approved it. SJD interpreted analyses, revised the manuscript, and approved it. KR developed the analysis plan, supervised and interpreted analyses, drafted parts of the manuscript, and approved it. YJL ran analyses and approved the manuscript. CCL ran analyses and approved the manuscript. AW helped draft the manuscript and approved it. GAG

interpreted the analyses, revised the manuscript, and approved it. JSF interpreted the analyses, revised the manuscript, and approved it. KR and CCL performed the statistical analyses and are independent of any commercial funder. They had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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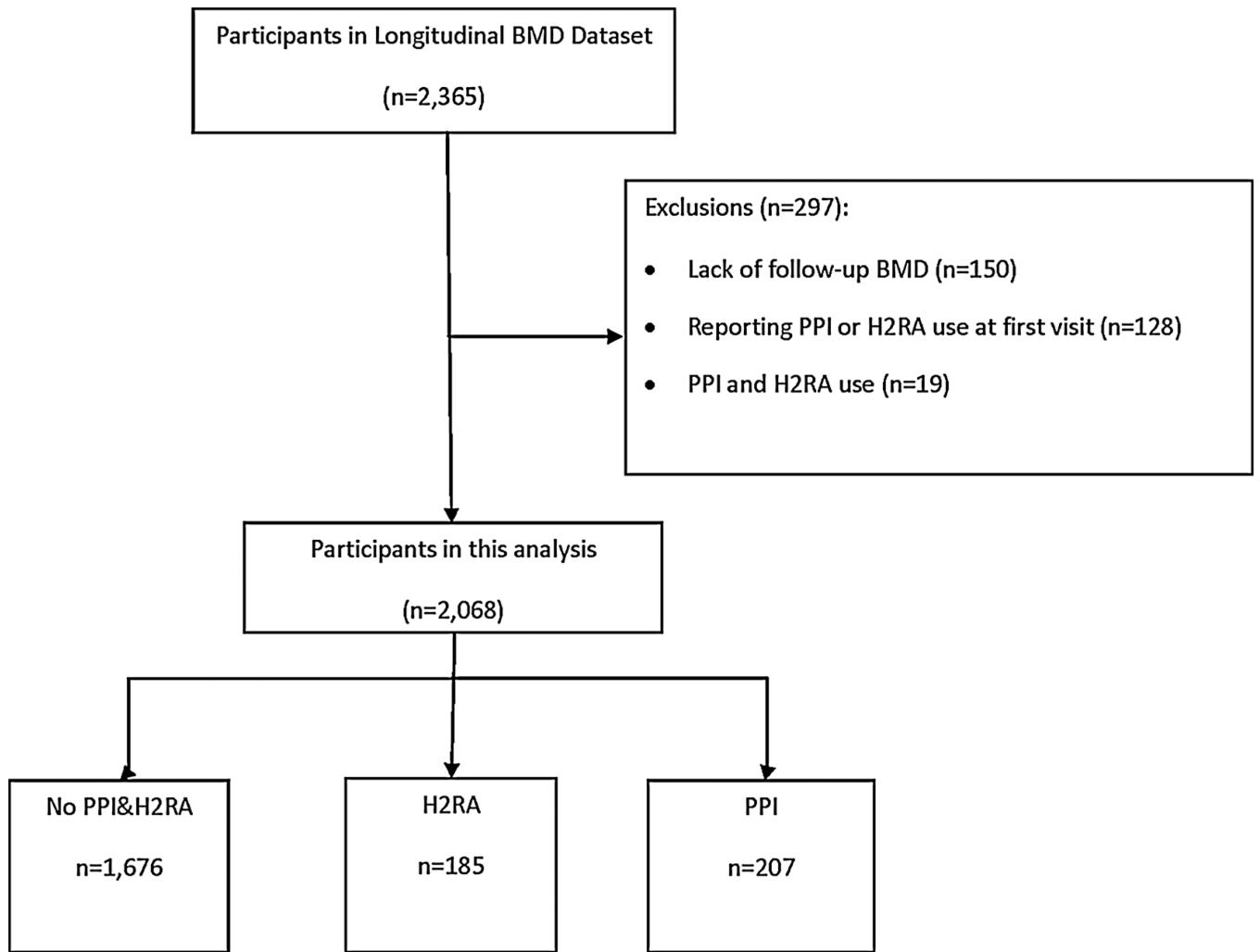


Fig. 1.
Study Cohort 1.

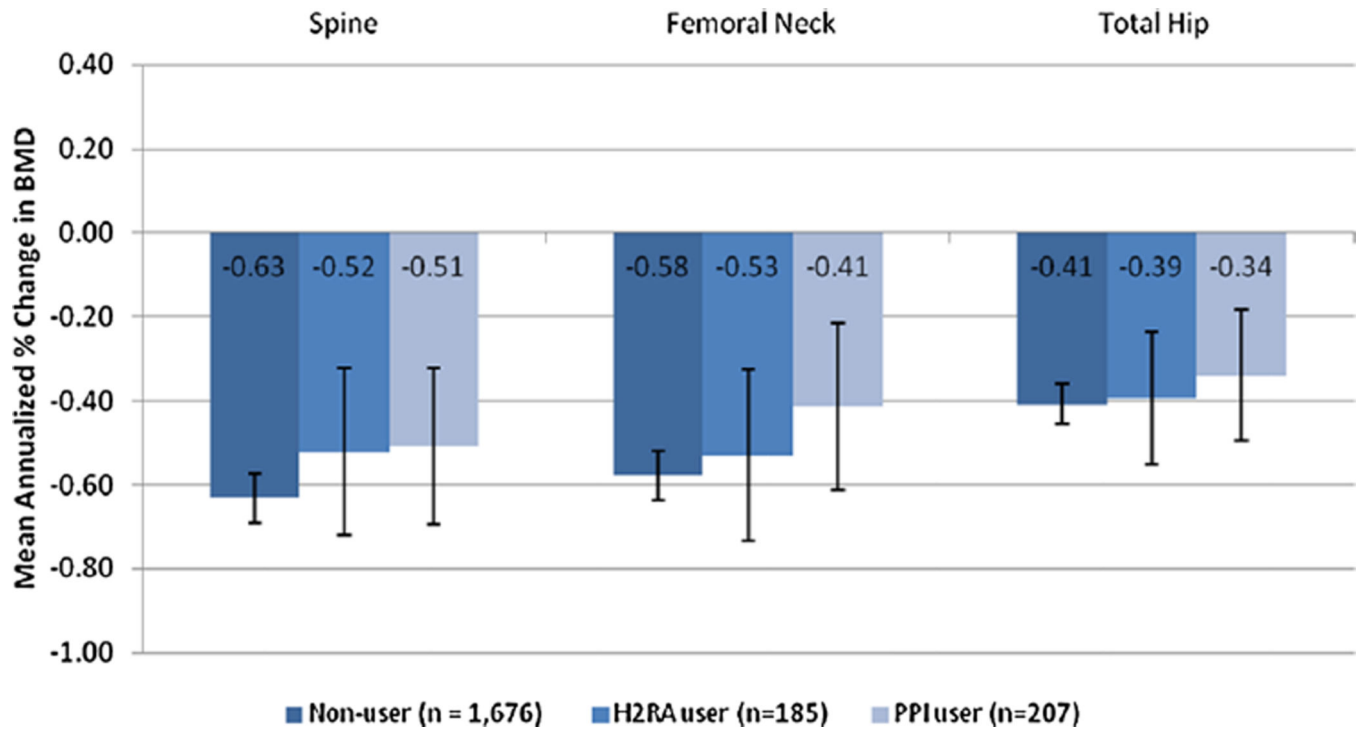


Fig. 2.
Mean annualized change in BMD in PPI users, H2RA users, and non-users in SWAN.

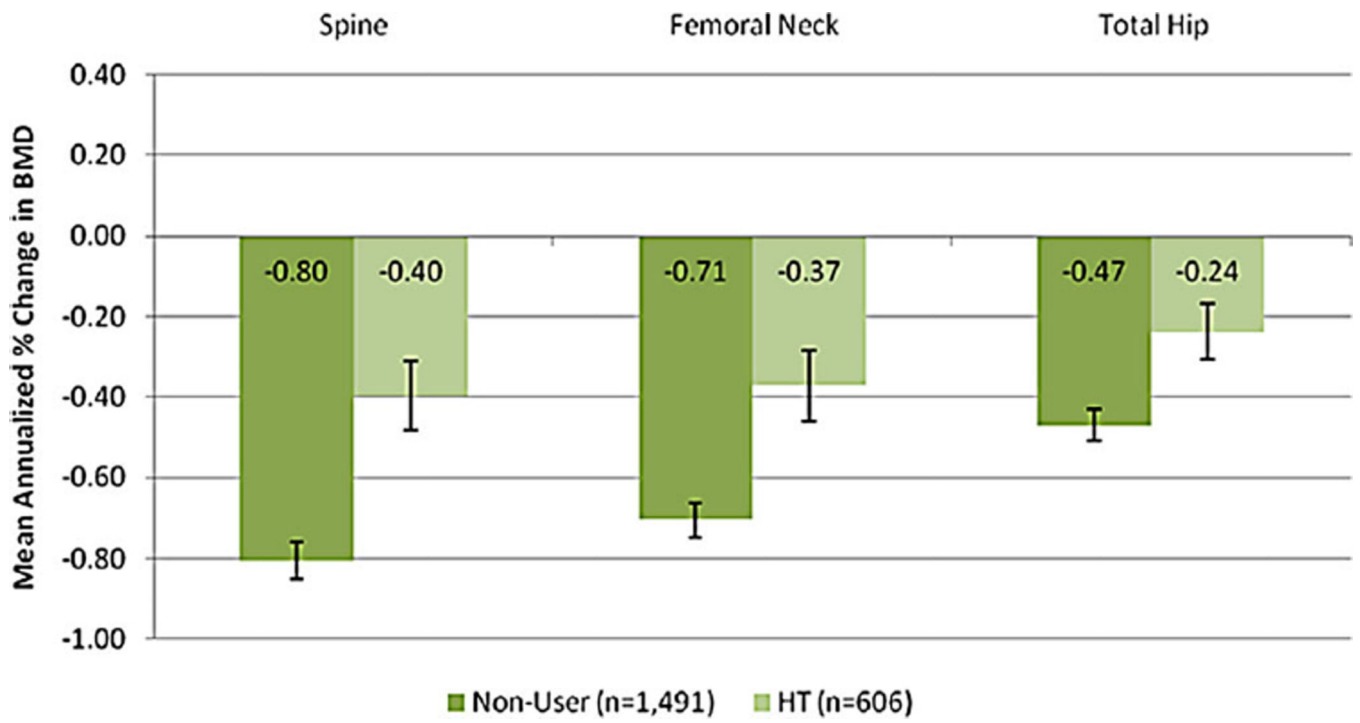


Fig. 3. Positive Control Analyses of Hormone Therapy Use Among Women in SWAN (cohort 2).

Table 1

Prior Longitudinal Studies Examining the Adjusted Relationship Between Proton Pump Inhibitors (PPI) and Bone Mineral Density (BMD)

Author (year)	Study population	PPI assessment	BMD assessment	Adjusted results ^{a,b}
Yu (2008) ⁽⁵⁾	<i>n</i> = 4230 men aged 65 years	PPI use defined as taking medication for previous 4 weeks to clinic visit.	SOF: baseline and 4.9 years later.	PPIs had no significant effect on change in BMD at total hip.
	<i>n</i> = 2856 women aged 65 years	SOF: baseline and 4.9 years later. MrOS: baseline and 4.6 years later.	MrOS: baseline and 4.6 years later.	Annual change in BMD:
	Subjects in the Osteoporotic Fractures in Men Study (MrOS) or women from the Study of Osteoporotic Fractures (SOF)		Assessed at the hip. Annualized % change.	Total hip: -0.70 (<i>p</i> = 0.08) (women) Total hip: -0.38 (<i>p</i> = 0.39) (men)
Targownik (2010) ⁽⁶⁾	<i>N</i> = 2549 subjects	Drug history for 5 years before baseline. PPI user if subject with use of PPI on 50% of the days (standard dose).	Change assessed for the lumbar spine and the total hip.	PPIs had no significant effect on change in BMD at standard or high-intensity doses.
	Subjects from the Manitoba Bone Mineral Density Database		Assessments separated by 1 to 3 years.	Annualized change in BMD:
			Annualized % change.	Spine: 0.03%±0.22% (<i>p</i> > 0.2) (standard dose PPI) Total hip: -0.17%±0.18% (<i>p</i> > 0.2) (standard dose PPI)
Gray (2010) ⁽⁸⁾	<i>n</i> = 6695 (hip); <i>n</i> = 6629 (spine)	Assessed at baseline and year 3. Duration of PPI use described as <1 year, 1 to 3 years, or >3 years.	Assessed at baseline and years 3 and 6	PPIs had no significant effect on change in BMD when time-varying PPI use was included.
	Women aged 50 to 79 years from Women's Health Initiative.		Assessed for total hip and spine.	Three-year changes in BMD including women on Ca/Vit D (PPI not considered as time-varying):
			Three-year % change.	Hip: 0.62 (PPI use) versus 1.36 (PPI non-use) (<i>p</i> = 0.05) Spine: 2.30 (PPI use) versus 1.34 (PPI non-use) (<i>p</i> = 0.94)
Targownik (2012) ⁽⁷⁾	<i>n</i> = 8340 completed baseline; <i>n</i> = 6458 completed 5-year assessment; <i>n</i> = 4512 completed 10-year assessment	Assessed at baseline, year 5, and year 10. PPI user if reported PPI use at all time points included in the analysis.	Assessed at baseline and years 5 and 10.	PPIs had no significant effect on change in BMD.
	Population-based stratified random sample of Canadian population (CaMOS) aged 25 years.		Assessed for femoral neck, total hip, and spine.	10-year change in BMD:
			10-year % change.	Hip: 0.9% (-1.0 to 2.9%) (<i>p</i> = NS) Femoral neck: -0.5% (-2.9 to 1.8%) (<i>p</i> = NS) Spine: -0.7% (-3.3 to 1.9%) (<i>p</i> = NS)

Note: Studies without a non-user group were excluded.

^aCovariates differed by study. Yu (2008) included age, race, BMI, alcohol use, exercise, corticosteroids, NSAIDs, calcium supplements, osteoporosis medications, self-reported health, concurrent weight change, initial total hip BMD, caffeine intake, smoking, and history of stomach surgery. Targownik (2010) included age, sex, BMI, cardiovascular disease, diabetes, hypertension, COPD, renal disease, cirrhosis, thyroid disease, alcohol abuse, inflammatory bowel disease, celiac disease, oral ERT, SERMs, calcitonin, bisphosphonates, systemic corticosteroids (>5mg prednisone per day), anti-androgens, tamoxifen, anti-epileptics, SSRIs, and thiazide diuretics. Targownik (2012) included age, sex, age-sex interactions, BMI, history of minimal trauma fracture, family history of minimal trauma fracture, presence of RA, IBD, CLD, CKD, thyroid disease, smoking, heavy alcohol use (14 drinks per week), history of falls, use of concomitant medications that may influence BMD (corticosteroids, thiazides β -blockers, nitrates, anti-epileptics, SSRIs, tamoxifen, and osteoporosis medications, total calcium intake, and vitamin D intake). Gray (2010) included age, race/ethnicity, BMI, smoking, physical activity level, self-reported health, parental history of hip fractures, diabetes mellitus, history of fractures, corticosteroid use, physical function construct, history of myocardial infarction or angina, history of asthma or emphysema, arthritis, osteoporosis, psychoactive medications use, past or current use of hormone therapy or bisphosphonates, moderate or severe stomach ulcers, moderate or severe heartburn, WHI trial participation, and intervention arms.

^bOnly results from adjusted longitudinal analyses are presented.

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Table 2

Baseline Characteristics of Three Groups Studied in Cohort 1

Characteristic	Non users (<i>n</i> = 1676)	H2RA users (<i>n</i> = 185)	PPI users (<i>n</i> = 207)	<i>p</i> Value
	<i>n</i> (%) or mean ± SD			
Age (years)	50.2 (±3.9)	49.6 (±4.0)	50.7 (±4.2)	<0.0001
Race/ethnicity				<0.0001
Black	421 (25.1)	49 (26.5)	79 (38.2)	
White	826 (49.3)	105 (56.8)	99 (47.8)	
Chinese	215 (12.8)	15 (8.1)	3 (1.5)	
Japanese	214 (12.8)	16 (8.7)	26 (12.6)	
Menopausal status				<0.0001
Surgical menopause	67 (4.0)	8 (4.3)	14 (6.8)	
Postmenopausal	392 (23.4)	35 (18.9)	66 (32.2)	
Late perimenopausal	109 (6.5)	13 (7.0)	23 (11.2)	
Early perimenopausal	724 (43.2)	73 (39.5)	67 (32.7)	
Premenopausal	278 (16.6)	32 (17.3)	22 (10.7)	
Hormone therapy	100 (6.0)	24 (13.0)	13 (6.3)	
Self-reported health status, <i>n</i> (%)				0.0003
Excellent or good	1444 (86.2)	143 (79.4)	167 (81.5)	
Fair	192 (11.5)	28 (15.6)	32 (15.6)	
Poor or very poor	23 (1.4)	9 (5.0)	6 (2.9)	
Current smoker	212 (12.7)	30 (16.5)	28 (13.7)	0.29
Calcium supplement use	997 (59.5)	99 (53.5)	129 (62.3)	0.21
Vitamin D supplement use	987 (58.9)	95 (51.4)	129 (62.3)	0.09
BMI (kg/m ²)	27.6 (±6.7)	30.4 (±7.4)	29.9 (±7.5)	<0.0001
Physical activity	7.83 (±1.61)	7.56 (±1.53)	7.35 (±1.63)	<0.0001
Bone mineral density (g/cm ²)				
Lumbar spine	1.16 (±0.24)	1.07 (±0.14)	1.07 (±0.16)	0.11
Femoral neck	0.78 (±0.12)	0.83 (±0.13)	0.83 (±0.13)	0.43
Total hip	0.94 (±0.20)	0.96 (±0.14)	0.97 (±0.14)	0.03
Comorbidities				
Heart attack/stroke/angina	5 (0.3)	0 (0.0)	3 (1.5)	0.16
Thyroid disease	138 (8.2)	18 (9.7)	29 (14.1)	0.04
Cancer	21 (1.3)	5 (2.7)	4 (2.0)	0.29
Diabetes	78 (4.7)	13 (7.0)	16 (7.8)	0.003
Osteoporosis	30 (1.8)	3 (1.6)	7 (3.4)	0.21
Vasomotor symptoms	802 (47.9)	105 (56.8)	131 (63.3)	<0.0001

Characteristic	Non users (n = 1676)	H2RA users (n = 185)	PPI users (n = 207)	p Value
Medication use at baseline				
Hormone therapy	200 (11.9)	36 (19.5)	30 (14.5)	0.0002
Bisphosphonate	22 (1.3)	2 (1.1)	6 (2.9)	0.15
Oral glucocorticoids	112 (6.7)	31 (16.8)	32 (15.5)	<0.0001
Thiazide diuretics	117 (7.0)	14 (7.6)	21 (10.1)	0.17

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Table 3
Mean Annualized Percent Change in Bone Mineral Density by Anatomic Site in Primary and Sensitivity Analysis Models

	Spine			Femoral neck			Total hip		
	Primary model ^a	Sensitivity analysis model ^b	Primary model ^a	Sensitivity analysis model ^c	Primary model ^a	Sensitivity analysis model ^d			
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)			
Non-user (n = 1605)	-0.61 (-0.67, -0.55)	-0.58 (-0.63, -0.52)	-0.46 (-0.51, 0.42)	-0.45 (-0.50, -0.40)	-0.32 (-0.36, 0.27)	-0.31 (-0.35, -0.26)			
H2RA user (n = 185)	-0.54 (-0.68, -0.39)	-0.51 (-0.65, -0.37)	-0.44 (-0.55, -0.33)	-0.45 (-0.56, -0.34)	-0.37 (-0.47, -0.26)	-0.36 (-0.47, -0.25)			
PPI user (n = 207)	-0.53 (-0.68, -0.38)	-0.48 (-0.62, -0.33)	-0.43 (-0.54, -0.32)	-0.41 (-0.53, -0.29)	-0.41 (-0.52, -0.29)	-0.38 (-0.49, -0.27)			

^aMain model adjusted for age, menopausal status, site, race, and BMI.

^bSpine MV model = primary model variables, smoking, diabetes, cancer, osteoporosis, vasomotor symptoms, hormone therapy, and bisphosphonate and thiazide diuretic use.

^cFemoral neck MV model = primary model variables, income, education level, physical activity, cancer, diabetes, hormone therapy, and bisphosphonate and thiazide diuretic use.

^dTotal hip MV model = primary model variables, education level, physical activity, cancer, diabetes, hormone therapy, and bisphosphonate and thiazide diuretic use.