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Effects of Analgesics on Bone Mineral Density: a Longitudinal Analysis of the Prospective SWAN Cohort with Three-group Matching Weights

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Abstract

PURPOSE—To examine the effects of analgesics on bone mineral density (BMD), which have not been examined in a longitudinal study with multiple measurements.

METHODS—We investigated changes in BMD associated with new use of analgesics in a prospective longitudinal cohort of mid-life women. BMD and medication use were measured annually. We compared BMD among new users of acetaminophen, NSAIDs, and opioids. Adjustment for baseline covariates was conducted through propensity score matching weights.

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On-treatment analysis was conducted with inverse probability of censoring weights. Analysis based on the initial treatment group was also conducted to provide insights into selection bias. Repeated BMD measurements were examined with generalized estimating equations.

RESULTS—We identified 71 acetaminophen new users, 659 NSAID new users, and 84 opioid new users among 2,365 participants. In the on-treatment analysis, the opioid group in comparison to the acetaminophen group had an additional average BMD decline of -0.06% [$-1.24, 1.11$] per year in the spine and -0.45% [$-1.51, 0.61$] per year in the femoral neck. BMD mean trajectories over time suggested a fifth-year decline in the opioid persistent users compared to other two groups. In the initial treatment group analysis, all three groups showed similar trajectories.

CONCLUSION—The BMD decline over time was similar among the three groups. However, five years of continuous opioid use may be associated with a greater BMD decline than five years on other analgesics. Further studies examining the relationship between very long term persistent opioid use and BMD are warranted.

Keywords

analgesics; bone mineral density; osteoporosis; propensity score; matching weights

INTRODUCTION

Many classes of drugs have been linked to increased risk of fractures or reduced bone mineral density (BMD). Histamine H2 receptor antagonists¹, opioids, and anticonvulsants² were among them. The cross-sectional nature of these studies, however, limit the assessment of temporality. Additionally, long-term effects of analgesics on bone health are not well understood.

Opioids have been associated with increased fracture risks in multiple longitudinal studies^{3–8}. The increased risks occurring soon after initiation^{4,6} suggest the primary mechanism is through acute neurologic effects, such as gait imbalance. However, chronic opioid use may also have indirect effects via endocrine changes^{9–11}; for example, hypogonadotropic hypogonadism has been found in patients receiving methadone maintenance therapy¹². Several studies also suggest lower BMD in opioid users^{13–15}. However, these studies were cross-sectional, had limited control of confounding, and focused on a particular subset of chronic opioid users (*i.e.*, former heroin addicts on methadone maintenance).

NSAID use has been associated with higher BMD in two cross-sectional studies^{16,17} adjusted for potential confounders such as body weight, although a more recent study found increased fracture risk among NSAID users despite stable BMD⁵. Both selective and non-selective NSAIDs exhibit anti-inflammatory properties through inhibiting cyclooxygenase(COX)-2, an enzyme that plays a role in prostaglandins synthesis. Prostaglandins, in turn, play important roles in both bone formation and bone resorption¹⁸.

The Study of Women's Health Across the Nation (SWAN)^{19,20} allows for rigorous assessment of the effects of analgesics on BMD because of its longitudinal design and repeatedly measured BMD. We hypothesized that opioids and NSAIDs are associated with

BMD reduction compared to acetaminophen (active control). Presence of three treatment groups of quite different sizes as well as frequent treatment changes posed challenges in analysis. Thus, we used recently proposed matching weights in a multiple group setting^{21,22} along with inverse probability of censoring weights over time²³.

METHODS

Study population and design

SWAN^{19,20}, a prospective longitudinal, community-based cohort study of mid-life women, enrolled participants in their pre-menopause between 1996 and 1997 from 8 U.S. sites to observe the natural history of menopause. Eligibility criteria included age 42–52 years old, at least one menstrual period within the past three months, and no hormonal medication use within the last three months. The SWAN BMD substudy enrolled 2,365 women of four racial/ethnic groups (1,177 Caucasian, 665 African American, 273 Japanese, and 250 Chinese) with approximately annual BMD measurement. Longitudinal follow-up is still ongoing, and SWAN data collection consists of physical measures, fasting morning blood draw, interviewer-administered and self-administered questionnaires (completed at home or in clinic). Participants gave written informed consent and study sites obtained institutional review board approval.

Exposure assessment

The exposure of interest was the type of analgesic—opioid, NSAID including COX-2 selective inhibitors, and/or acetaminophen—that participants took at 2 consecutive annual visits. The individual-specific baseline visit was defined as the visit immediately before the first of these consecutive visits. Medication use, including both prescription and over the counter (OTC), was ascertained through interviewer-administered questionnaire for medications used twice or more per week during the past month and was then verified by inspection of medication containers. The exposure definition was constructed *hierarchically* (eTable 1): opioid user if an opioid is used regardless of the other two; NSAID user if an NSAID is used but not opioids regardless of acetaminophen; and acetaminophen user if it is the only analgesic used. Participants who transitioned between these exposure categories were assigned the exposure status at the time when they first met the eligibility criteria.

Outcome assessment

Details of the BMD measurements have been described in previous studies using SWAN^{24–26}. BMD (g/cm²) was measured in the lumbar spine and femoral neck at each study visit. Raw BMD measurements were converted to baseline-normalized %BMD values for interpretability, as regularly done in major osteoporosis clinical trials^{27–30}. That is, for each individual, the outcome was defined as 100% at the individual-specific baseline visit when the covariates were ascertained (year 0), and subsequent values were described in relation to this baseline value (e.g., 96% of the baseline value at year 4). Follow-up was truncated at year 5 because very few people remained in the initial treatment categories beyond that point.

Covariate assessment

Covariates were assessed at the individual-specific baseline visit. Body mass index (BMI) was calculated from height and weight at the study baseline. The demographic variables included age, race/ethnicity, self-reported annual income (low [$\leq$ \$19,999], medium [\$20,000–49,999], and high [$\geq$ \$50,000-]), and college education (yes/no). Alcohol intake (none/low [< 1 drink/month], moderate [up to 1/week], and high [≥ 2 /week]), current tobacco use (yes/no), and physical activity measures were available as lifestyle variables. Physical activity was measured using the modified Baecke Physical Activity Questionnaire (range 3–15, with lower scores indicating less exercise)^{31,32}. Self-reported comorbidities included thyroid disease, diabetes, and history of cancer. Self-reported pain-related quality of life (range 0–100, with 100 indicating excellent quality of life³³), vasomotor symptoms, and overall perception of health were also reported. Medications included hormone therapy for menopause, bisphosphonates, calcium supplements, vitamin D supplements, and oral glucocorticoids. Menopause transition (MT) stage was defined based on menstrual cycles²⁵ (eTable 2). We created four categories of MT stages for the main analysis: pre- or early perimenopause; late perimenopause; postmenopause; and unknown (eTable 2). We also conducted a subgroup analysis among those who had a known date of the final menstrual period (FMP), using MT stages based on time prior to or after the FMP (eTable 3).²⁴

Statistical analyses

Participant characteristics at the study baseline were summarized within each exposure group. To examine between group imbalance in the unmatched cohort of patients, the standardized mean differences (SMD)³⁴ were calculated in each pairwise treatment contrast and then averaged across all three contrasts. The SMD represents how different groups are for a given covariate. Covariates that have SMD ≤ 0.1 are considered reasonably balanced³⁴. We multiply imputed missing covariates via the *mice* R package.^{35,36}

Multinomial logistic regression was used for the propensity score (PS) model because the exposure status had three categories (acetaminophen, NSAIDs, or opioids)³⁷, resulting in one PS for each exposure category. All baseline covariates listed in the baseline table (Table 1) were included as explanatory variables. We used the PSs as *matching weights* (MW; eAppendix Methods), a PS weighting method proposed by Li and Greene²¹. A recent study generalized MW to multiple treatment group settings²². Compared to 1:1:1 PS matching, MW allows for retention of all subjects, which is a potential advantage when the group sizes are dissimilar. Compared to the conventional inverse probability of treatment weights (IPTW), the target of inference focuses on those who are in clinical equipoise among all drugs (i.e., similar estimand to PS matching). This clinical equipoise estimand was more stably estimated in the settings where baseline covariates were more different among groups²².

MW, as it is known currently, is only applicable to time-invariant exposure. However, a drug exposure is typically time-varying. Therefore, we used the *on-treatment analysis* and *initial treatment group analysis* to make treatment group assignment effectively time-invariant. The main analysis was *on-treatment* analysis of those who remained in the initial treatment category (adherers). That is, those who deviated from their initial category were censored at

the time of deviation, making the treatment assignment effectively time-invariant among uncensored time points remaining in the analysis dataset. We additionally censored patients at the initiation of hormone therapy for menopause or bisphosphonate or cancer diagnosis. Such censoring of participants who deviate from the initial treatment status or started bone active medications can introduce selection bias –those who are censored and retained may not share the same risks for BMD changes. Thus, we additionally assigned time-varying inverse probability of censoring weights (IPCW)²³ to ameliorate this selection bias issue using the same set of covariates as the time-invariant MW model, but updated for each time point. A final weight for a given time point was constructed as the product of the individual-specific time-invariant MW and the individual-specific, time point-specific time-varying IPCW and was normalized to represent the sample size of each treatment group at each time point.³⁸ This approach should estimate the effect of continuous treatment,^{23,39} assuming both MW for baseline confounding by indication and IPCW for selection bias introduced by artificial censoring are successful. We also conducted an alternative analysis based on the initial treatment category at the study baseline (*initial treatment group* analysis). Participants remained in their original treatment category regardless of subsequent medication changes in this analysis, also making the treatment variable time-invariant. This approach is an observational analogue of the intention-to-treat analysis used in clinical trials, and should estimate the effect of assigned treatment³⁹, assuming MW for baseline confounding by indication is successful. Censoring also occurred administratively because some subjects started analgesics late in the SWAN study, thus, reaching the latest SWAN visit (visit 13) before having the fifth-year visit after analgesic initiation. This type of administrative censoring was assumed non-informative.

The mean baseline-normalized %BMD over time for the spine and femoral neck were plotted in both the on-treatment analysis and initial treatment group analysis. We used the generalized estimating equation with the auto-regressive correlation structure to account for weighting and the clustering of repeated BMD measurements within each individual during follow-up. Confidence intervals were calculated based on robust sandwich standard error estimates. The time effect on the mean baseline-normalized %BMD was modeled as a linear term to provide average yearly change estimates. The slope differences of interest, NSAIDs versus acetaminophen, and opioids versus acetaminophen, were incorporated into the model as time-group interaction terms. We repeated the analyses in the FMP subgroup. We also repeated the main analysis after excluding an outlying data point as a sensitivity analysis. Another sensitivity analysis for the outcome model further adjusted for variables that had SMD > 0.1 after balancing by MW.

RESULTS

Study population

Among 2,365 participants in the SWAN BMD cohort, 71 acetaminophen new users, 659 NSAID new users, and 84 opioid new users were identified (eFigure 1; break down by generic names in eTable 4). Their unadjusted baseline characteristics are shown in Table 1. The most prominent baseline differences were noted for pain-related quality of life (QoL), ethnic composition, income, overall perception of health, BMI, femoral neck BMD, and

physical activity. The pain-related QoL was lower for the opioid users (48.8) compared to the other two groups that had scores around 70. Femoral neck BMD was higher in the opioid group than the other groups likely associated with their higher BMI. Physical activity was highest among NSAID users and was lowest among opioid users. Twenty-six percent of NSAID users were also exposed to acetaminophen. Opioid users also had substantial concurrent exposure (acetaminophen 80% and NSAIDs 66%). Matching weights reduced group imbalance at the baseline (Table 2), even in comparison to other PS methods (eFigure 2)^{40,41}. The mean follow-up durations were similar across treatment groups (eTable 5).

Adjusted main analysis using menstrual period-defined stages

Figure 1 shows the mean baseline-normalized BMD over the five-year follow-up period for each treatment group (n = 814) as well as the treatment group contrasts from the generalized estimating equation (see eFigure 3 for unadjusted counterpart). The mean annual change in each treatment group as well as group differences in slopes are shown in Table 3.

The on-treatment analysis (Figure 1, left panels) was suggestive of a greater decline in BMD in the opioid group compared to the acetaminophen group, principally at the fifth year. The opioid group in comparison to the acetaminophen group had an additional mean BMD decline of -0.06% [$-1.24, 1.11$] per year in the spine and -0.45% [$-1.51, 0.61$] per year in the femoral neck. The initial treatment group analysis, on the other hand, demonstrated more similar trajectories for all three groups (Figure 1, right panels). The difference between the opioid group and the acetaminophen group diminished to -0.06% [$-0.66, 0.78$] in the spine and to 0.08% [$-0.65, 0.82$] in the femoral neck.

Adjusted final menstrual period-based analysis

eFigure 4 shows the corresponding outcome analysis in the subgroup of women with a known FMP date (n = 471). The adjustment for the menopause transition stages at individual-specific baseline visit was based on the time prior to or after FMP (pre-transmenopause, transmenopause, or postmenopause; eTable 3)²⁴. The baseline characteristics before propensity score weighting are in eTable 6. Propensity score weighting improved covariates balance, but to a lesser extent than in the main cohort (eTable 7). The mean trajectories were less stable due to the smaller sample size, particularly in the on-treatment analyses. The mean annual change in each treatment group is shown in eTable 8. The on-treatment analyses exhibited overlapping mean trajectories (eFigure 4, left panels). The initial treatment group analyses (eFigure 4, right panels) produced trajectories with more separation than the main initial treatment group analyses (Figure 1, right panels).

Sensitivity analysis

As the main on-treatment analysis showed a strong fifth-year deflection in the trajectory, we examined for the presence of outliers. One subject with probable thyroid disease exhibited an outlying decline trajectory. This subject remained in the opioid category for the full five years without meeting any of the censoring criteria, thus, she was gradually up-weighted over time via IPCW, becoming more influential. Reanalysis excluding this subject (eFigure 5) resulted in a less prominent decline in the fifth year, although the opioid group remained

the lowest group at the fifth year. Outcome analysis further adjusting for the sub-optimally balanced variables gave similar estimates of group differences in slopes (eTable 9).

DISCUSSION

In the current study, we examined the association between analgesic use and BMD decline over time in a well-established cohort of mid-life women, with a focus on the contrasts between opioids and acetaminophen as well as NSAIDs and acetaminophen. We used three-group MW for baseline covariate balancing and time-varying IPCW to reduce selection bias by artificial censoring over time. To our knowledge, the current study is the first instance of MW used in conjunction with IPCW in the multiple treatment group setting. The average slope differences were not statistically significant in both on-treatment analysis and initial treatment group analysis. However, the on-treatment analysis was suggestive of a potentially greater decline in the BMD in the opioid group compared to the acetaminophen group after five years of continuous use. The trajectory of BMD decline in the NSAID group was similar to the acetaminophen group. Between-group differences were not clearly observed in the initial treatment group analysis.

There is no established gold standard for the clinically meaningful group difference in BMD changes over time, however, several clinical trials were summarized in eTable 10 to give some idea^{27–30}. In the FIT study²⁷, which demonstrated hip fracture reduction, the annual slope difference in the femoral neck BMD was +1.0%/year in the alendronate group compared to the placebo group. Our study found that the annual slope difference was –0.45%/year [–1.51, 0.61] for the femoral neck BMD comparing the opioid new users to the acetaminophen new users (Figure 1), which was not statistically significant, but did not rule out 1.0% difference in annual slopes. The five-year difference in BMD comparing the opioid group to the acetaminophen group was close to –10% in the on-treatment analysis although the difference was negligible in the initial treatment group analysis (Figure 1). The noticeable discrepancy between the on-treatment analysis and the initial treatment group analysis suggests the contribution of residual selection bias that was not fully controlled by IPCW, likely due to the small size of the opioid arm that remained on treatment, in addition to the exposure misclassification in the initial treatment group analysis. However, even in the sensitivity analysis removing an outlying observation, some group difference in the range of –3 to –5% remained, which may suggest a potentially greater decline in BMD among persistent opioid users.

Although the longitudinal association of opioid use and fractures has been well documented in multiple studies^{3–8}, the association of opioid use and lower BMD has been shown only in cross-sectional studies^{13–15}. To our knowledge, only one study has examined the longitudinal effect of opioids on BMD⁵ and reported no clinically relevant longitudinal association based on BMD measurements ten years apart. Our study provides additional insight into the potential effect of opioids on BMD by providing more granular follow-up, although this study alone is not conclusive. Past cross-sectional studies that demonstrated an association between opioid use and lower BMD were among former opioid abusers undergoing methadone therapy, whereas the current study was among community-dwelling healthy women.

Several studies have suggested potentially beneficial effects of NSAIDs on BMD. Bauer *et al.* found a cross-sectional association between higher BMD and current frequent NSAID use compared to infrequent use and non-use in their 1996 study on community-dwelling women aged at least 65 years old¹⁶. Carbone *et al.*¹⁷ examined the cross-sectional association between NSAID use and BMD in the Health ABC study among community-dwelling men and women 70–79 years of age. They found that current users of COX-2 selective NSAIDs with concurrent aspirin use had higher BMD than non-users. A 10-year longitudinal study by Vestergaard *et al.*⁵, which also examined acetaminophen, NSAIDs, and opioids, found a very minor (clinically insignificant) increase in spine and whole body BMD among NSAID users compared to non-users. The current study showed essentially identical BMD trajectories between NSAID users and acetaminophen users in both the on-treatment analysis and the initial treatment group analysis.

SWAN was designed to characterize the biological, symptomatic, and psychosocial changes that occur during the menopausal transition and their effects on women's health and well-being. Thus, our findings may not generalize to men, or to women in different age ranges. SWAN did not specifically enroll analgesic users, thus, the number of users was small, limiting our ability to draw firm conclusions. Also SWAN does not have reliable medication dosage information. Doses of opioids can be highly variable among opioid users due to the highly individualized nature of these prescriptions⁴². However, high-dose opioid use is unlikely in this population cohort of generally healthy mid-life women.

Our longitudinal study design has some unique strengths compared to the prior cross-sectional studies on this topic. Use of acetaminophen as a comparator medication–active comparator design⁴³– ensured that all three treatment groups had at least some pain. Non-users – individuals who do not use analgesics – are expected to have much less pain than analgesic users, thus using such a comparator group without pain could induce a spurious association between BMD changes and medication use⁴⁴, which can be difficult to control for. We also used a new user design⁴³, which examines subjects starting the medication of interest, in an attempt to parallel the design of a hypothetical clinical trial⁴⁵ and ensures that the baseline covariates were measured before medication initiation.

As a safety outcome study, the primary effect of interest is the on-treatment effect³⁹, that is the effect of medication on the outcome if subjects were made to adhere to the regimen²³. However, the naïve on-treatment analysis that simply censors subjects who do not follow the initial regimen of interest often introduces selection bias⁴⁶. Therefore, we used IPCW to account for selection. The study revealed a difficulty of IPCW in the presence of small number of subjects in each arm. One of the few persistent opioid users happened to have an outlying decline in BMD, thereby exerting increasing influence at later time points because of progressively greater IPCW. Some of the differences in BMD trajectories, however, persisted after excluding this subject. Examination of the very long-term on-treatment effect beyond 5 years was not possible due to the very few adherers, potentially limiting the scope of the study.

In conclusion, the average BMD slope differences over a five-year period were not statistically significant among mid-life female analgesic new users. However, five years of

persistent opioid use may be associated with a greater BMD decline. It is important to remember that chronic opioid use, although becoming common, is not a well-justified practice in the setting of non-cancer pain^{47,48}. Further studies examining the relationship between very long term persistent opioid use and BMD as well as their dose response are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

1. Three-group matching weights are modified propensity score weights that emulate three-way simultaneous matching.
2. Matching weights balanced covariates reasonably across three groups with size imbalance.
3. We observed a potential decrease in bone mineral density among mid-life women who remained on opioids for five years compared to users of acetaminophen.

Figure 1. Group mean trajectories of baseline-normalized % bone mineral density (BMD)

The numbers at the bottom of each panel are number of individuals contributing BMD measurements (Top: Acetaminophen, Middle: NSAIDs, and bottom: Opioids). On-treatment analysis censored patients at the time they changed analgesic categories, whereas initial treatment group analysis retained these patients in the initial treatment groups.

Abbreviations: NSAID: non-steroidal anti-inflammatory drug; N vs A: NSAID group vs Acetaminophen group; O vs A: Opioid group vs Acetaminophen group; Spine: lumbar spine BMD; Time Since Baseline: Time since the baseline visit in years.

Table 1Baseline characteristics of analgesics new users *before* propensity score weighting.

	APAP users	NSAID users	Opioid users	SMD
N	71	659	84	
Age (mean (SD))	49.34 (4.33)	49.43 (4.02)	50.63 (4.42)	0.200
Ethnicity (%)				0.493
Caucasian	33 (46.5)	385 (58.4)	40 (47.6)	
Black	25 (35.2)	191 (29.0)	43 (51.2)	
Asian	13 (18.3)	83 (12.6)	1 (1.2)	
Income (%)				0.383
Low (<19k)	9 (15.5)	46 (7.9)	13 (20.0)	
Middle (20k–49k)	16 (27.6)	203 (34.7)	28 (43.1)	
High (50k+)	33 (56.9)	336 (57.4)	24 (36.9)	
College education (%)	26 (36.6)	302 (46.2)	23 (27.7)	0.260
BMI (mean (SD))	28.43 (8.23)	29.16 (7.19)	32.43 (7.25)	0.354
Physical activity [3–15] (mean (SD))	7.49 (1.51)	7.87 (1.65)	7.08 (2.08)	0.295
Vasomotor symptoms (%)	34 (49.3)	341 (52.2)	47 (56.0)	0.089
Menopause transition stage (%)				0.318
Pre/Early Peri	45 (63.4)	458 (69.5)	41 (48.8)	
Late Peri	3 (4.2)	43 (6.5)	6 (7.1)	
Post	16 (22.5)	108 (16.4)	26 (31.0)	
Unknown	7 (9.9)	50 (7.6)	11 (13.1)	
Lumbar spine BMD g/cm² (mean (SD))	1.04 (0.14)	1.08 (0.15)	1.11 (0.16)	0.291
Femoral neck BMD g/cm² (mean (SD))	0.81 (0.13)	0.85 (0.14)	0.88 (0.14)	0.340
Pain-related QoL [0–100] (mean (SD))	70.44 (18.26)	69.75 (19.74)	48.77 (25.35)	0.647
Overall perception of health (%)				0.386
Same	28 (42.4)	270 (43.1)	30 (40.0)	
Better	31 (47.0)	297 (47.4)	22 (29.3)	
Worse	7 (10.6)	60 (9.6)	23 (30.7)	
Alcohol (%)				0.177
None/Low	34 (56.7)	285 (47.1)	34 (50.7)	
Moderate	16 (26.7)	168 (27.8)	21 (31.3)	
High	10 (16.7)	152 (25.1)	12 (17.9)	
Current smoker (%)	14 (20.3)	96 (14.7)	21 (25.0)	0.173
Thyroid disease (%)	9 (13.4)	66 (10.1)	10 (11.9)	0.069
Diabetes (%)	6 (8.5)	34 (5.2)	16 (19.0)	0.292
Calcium supplement (%)	21 (29.6)	216 (32.8)	18 (21.4)	0.171
Vitamin D supplement (%)	15 (21.1)	105 (15.9)	8 (9.5)	0.218
Oral glucocorticoids (%)	3 (4.2)	14 (2.1)	2 (2.4)	0.080

Missing proportions: BMI 7%; Income 13%; College education 1%; Physical activity 52% (not measured at every visit by design); Vasomotor symptoms 1%; BMD 10%; Pain-related QoL 15%; Alcohol 11%; Smoking 1%; Cancers 1%; Thyroid disease 1%.

Abbreviations: APAP: acetaminophen; NSAID: non-steroidal anti-inflammatory drug; SMD: standardized mean difference; BMI: body mass index; Menopausal status: menopausal status define by menstrual cycles (See eTable 2); BMD: bone mineral density in g/cm^2 ; QoL: quality of life.

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Table 2Baseline characteristics of analgesics new users *after* propensity score weighting.

	APAP users	NSAID users	Opioid users	SMD
Age (mean (SD))	49.25 (3.72)	49.66 (4.23)	49.73 (4.27)	0.086
Ethnicity (%)				0.103
Caucasian	53.9	54.0	50.6	
Black	41.7	43.4	46.9	
Asian	4.4	2.6	2.5	
Income (%)				0.121
Low (<19k)	16.3	19.4	20.2	
Middle (20k–49k)	33.7	34.2	37.6	
High (50k+)	50.0	46.5	42.2	
College education (%)	37.0	32.0	31.1	0.085
BMI (mean (SD))	30.79 (7.87)	30.56 (7.35)	30.66 (6.54)	0.031
Physical activity [3–15] (mean (SD))	7.25 (1.63)	7.26 (1.67)	7.45 (1.92)	0.089
Vasomotor symptoms (%)	46.7	54.6	55.7	0.125
Menopause transition stage (%)				0.155
Pre/Early Peri	61.8	58.8	57.1	
Late Peri	7.2	5.3	9.2	
Post	21.5	22.0	21.2	
Unknown	9.5	13.9	12.6	
Lumbar spine BMD g/cm² (mean (SD))	1.08 (0.14)	1.07 (0.15)	1.08 (0.14)	0.066
Femoral neck BMD g/cm² (mean (SD))	0.85 (0.13)	0.84 (0.13)	0.86 (0.12)	0.074
Pain-related QoL [0–100] (mean (SD))	65.17 (17.45)	62.66 (19.84)	63.84 (20.99)	0.088
Overall perception of health (%)				0.092
Same	40.4	44.8	39.7	
Better	42.7	38.5	43.8	
Worse	16.9	16.7	16.5	
Alcohol (%)				0.074
None/Low	52.0	50.0	49.2	
Moderate	32.8	32.2	34.0	
High	15.3	17.8	16.8	
Current smoker (%)	19.8	26.1	23.9	0.102
Thyroid disease (%)	10.2	14.6	12.4	0.091
Diabetes (%)	12.8	13.4	12.2	0.030
Calcium supplement (%)	16.5	22.6	21.8	0.106
Vitamin D supplement (%)	8.4	12.7	12.6	0.098
Oral glucocorticoids (%)	2.9	2.3	1.3	0.079

Abbreviations: APAP: acetaminophen; NSAID: non-steroidal anti-inflammatory drug; SMD: standardized mean difference; BMI: body mass index; Menopausal status: menopausal status define by menstrual cycles (See eTable 2); BMD: bone mineral density in g/cm²; QoL: quality of life.

Table 3

Main bone mineral density analysis results from generalized estimating equations.

Analysis Type	Site	Group	Mean Annual Change (%)	Group Difference (%)
On Treatment	Spine	Acetaminophen	−0.90 [−1.58, −0.21]	Ref.
		NSAIDs	−0.76 [−0.92, −0.59]	0.14 [−0.56, 0.85]
		Opioids	−0.96 [−1.92, −0.00]	−0.06 [−1.24, 1.11]
	Femoral Neck	Acetaminophen	−0.61 [−1.21, −0.02]	Ref.
		NSAIDs	−0.60 [−0.81, −0.39]	0.02 [−0.61, 0.64]
		Opioids	−1.07 [−1.95, −0.19]	−0.45 [−1.51, 0.61]
Initial Treatment	Spine	Acetaminophen	−0.72 [−1.13, −0.30]	Ref.
		NSAIDs	−0.79 [−0.93, −0.66]	−0.07 [−0.51, 0.36]
		Opioids	−0.66 [−1.25, −0.07]	0.06 [−0.66, 0.78]
	Femoral Neck	Acetaminophen	−0.82 [−1.28, −0.36]	Ref.
		NSAIDs	−0.64 [−0.80, −0.49]	0.18 [−0.30, 0.66]
		Opioids	−0.74 [−1.31, −0.16]	0.08 [−0.65, 0.82]

On-treatment analysis censored patients at the time they changed analgesic categories, whereas initial treatment group analysis retained these patients in the initial treatment groups.

Abbreviations: NSAID: non-steroidal anti-inflammatory drug; Ref.: Reference.