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Low Cumulative Disease Activity is Associated with Higher Bone Mineral Density in a Majority Latinx and Asian US Rheumatoid Arthritis Cohort

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Abstract

Objective: Prior studies have found conflicting results when evaluating the association between rheumatoid arthritis (RA) disease activity and bone mineral density (BMD). Whether or not cumulative RA disease activity is associated with BMD remains unanswered.

Methods: Data were from the University of California San Francisco RA Cohort from years 2006–2018. Those with BMD measures and at least two study visits prior to BMD measure were included in the study. The association between low cumulative disease activity, as measured by DAS28ESR, with the primary outcome of femoral neck BMD was assessed using multivariable linear regression. Sensitivity analyses were performed substituting CDAI for the disease activity measure as well as total hip and lumbar spine BMD as outcomes.

Results: 161 participants with RA were studied. The cohort was 62.4±10.2 years old and 88% female. Hispanic/Latino (N=73, 45%) and Asian (N=59, 37%) were the most common racial/ethnic groups in our cohort. Mean RA duration was 10.5±7.3 years and 83% were ACPA positive. Low disease activity was independently associated with higher femoral neck BMD compared to the moderate/high disease activity group (β= 0.071 [95%CI: 0.021 to 0.122], p=0.020). The relationship between low cumulative disease activity was similar when CDAI and other BMD sites were substituted in the multivariable models.

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Conclusion: Low cumulative disease activity as measured by DAS28ESR was associated with higher femoral neck BMD, independent of traditional osteoporosis risk factors (e.g., age, sex, BMI) in a unique RA cohort. Results were similar when evaluating cumulative low CDAI and other BMD sites.

Keywords

rheumatoid arthritis; osteoporosis; inflammation; bone; metabolic disease

Introduction:

Patients with rheumatoid arthritis (RA) have an increased risk for reduced bone mineral density (BMD) and osteoporotic fracture compared to the general population (1). RA is an independent risk factor for fracture in the Fracture Risk Assessment Tool (FRAX), which calculates 10-year risk of major osteoporotic and hip fractures (2). In the FRAX, RA is treated as a dichotomous variable(2), however, RA is a heterogeneous disease with a wide range of disease severity and variable responses to therapies (1,3–7). Therefore, the effect of RA on BMD is unlikely to be the same across the disease spectrum, yet the diagnosis of RA carries the same degree of risk in each person in which FRAX is applied. Currently, clinicians cannot accurately predict which individual RA patients are at highest risk for low BMD and fracture.

Risk factors for low BMD and osteoporotic fracture in RA have been attributed to a combination of primary effects of the disease and medications used to treat it, notably glucocorticoids (GCs)(1,3,4,6). It is known that RA disease severity, represented by various measures, such as disease duration, erosive disease or functional status, have negative associations with BMD (5,8–13). Prior studies evaluating the association between RA disease activity and BMD have shown conflicting results and have not used modern ACR recommended RA disease activity measures (14). They have also employed baseline disease activity or a mean of disease activity (15,16) to predict BMD change over shorter time periods (17–21), which may not accurately represent cumulative RA disease activity nor be of sufficient time to detect differential effects on BMD between groups. Whether or not cumulative RA disease activity is associated with BMD remains unanswered.

In an effort to better understand individual risk for BMD in RA, we evaluated whether cumulative disease activity, measured by the Disease Activity Score 28 Joints with Erythrocyte Sedimentation Rate (DAS28ESR), is an independent risk factor for BMD in a longitudinal US RA cohort comprised of racial and ethnic groups traditionally underrepresented in research.

Methods:

Data were from the University of California, San Francisco (UCSF) RA Cohort, an observational cohort established in 2006. The UCSF RA cohort has two clinical sites, the university and the safety-net hospital clinic which cares for a people from racial and ethnic groups that are underrepresented both in the United States population and in RA research. To be included in this analysis, participants needed to be followed at the safety-

net hospital clinic and have at least two disease activity score-28 joints with erythrocyte sedimentation rate (DAS28ESR) measures preceding a dual-energy x-ray absorptiometry (DXA)-based BMD measurement prior to June 30th, 2018. DXAs were ordered based both on the 2014 National Osteoporosis Foundation (NOF) guideline (22), which recommends BMD screening those with RA at age 50 and for those on at least 5 mg daily prednisone for at least 3 months. Additionally, DXAs were ordered on cohort participants of any age by the discretion of the treating rheumatologist based on additional risk factors. 161 of 387 (41%) participants met the inclusion criteria for this analysis. The group who was studied was significantly older than that excluded (65.1±10.3 vs. 58.5±15.2 years, $p<0.001$) but did not differ based on sex and race.

The primary outcome was femoral neck BMD (g/cm^2). This site was chosen because it is the least affected by degenerative changes as compared to the lumbar spine and total hip site. To maximize the observation time for individual participants, the most recent DXA scan was used for our analyses. Data up until the DXA scan were summarized to create a cross-sectional dataset. Our primary predictor was cumulative disease activity as measured by DAS28ESR. Use of the mean can be heavily influenced by outliers and standard AUC can either over- or underestimate cumulative exposure because it assumes stable levels between observations. We therefore calculated cumulative disease activity during the study using trapezoidal area under the curve (AUC) method (23). The trapezoidal method provides a more accurate estimate of the cumulative exposures compared to traditional rectangular method because at assumes a gradual change to the next timepoint, rather than carrying forward the value from the previous observation (Figure 1). Because participants had different observation periods, the cumulative disease activity was divided by observation time. We hypothesized that low disease activity would be associated with improved BMD and therefore dichotomized the DAS28ESR category. The resultant groups were remission/low disease activity (≤3.2) and moderate/high disease activity (>3.2) (14). Sex and race/ethnicity were obtained by self-report and categorized as Hispanic/Latino, Asian and Other. RA duration was defined as time from diagnosis. Prednisone usage was also modeled by trapezoidal AUC because mean values could be heavily influenced by prednisone “bursts” used for RA flares. Biologic disease modifying antirheumatic drug (bDMARD) represented the following drug categories: tumor necrosis factor inhibitor, anti-IL6 agent, anti-CD19 agent, CTLA4 and janus kinase inhibitor. Ever exposure to bDMARDs was used to describe the cohort. Because doses of bDMARDs are not directly comparable, we modeled bDMARD exposure as the proportion of visits exposed which was used in our multivariable analysis. Similarly, ever-exposure to and proportion of visits using conventional DMARDs (cDMARDs) was calculated for those on methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. We used proportion of visits for DMARD exposure because a small proportion of participants had periods of time without a study visit. During these periods, it is likely the participant did not have DMARDs refilled due to missing monitoring labs, yet prednisone was assumed to be filled as it is often filled by non-rheumatology providers (e.g. primary care). Osteoporosis medication use was collected through the electronic medical record and, because some patients receive primary care outside of the hospital system, it was also queried of participants. One patient was exposed to a PTH analogue and 3 to selective estrogen receptor modulators, each of these were all

also exposed to bisphosphonate and were included in the osteoporosis medication exposed group. Given the inability to distinguish exact duration of exposure and the long half-life of bisphosphonates, osteoporosis medication use was represented as ever or never use. BMD T-scores at each site were calculated to describe the cohort.

Missing data were imputed by using multiple imputation with chained equations with 10 imputations. Variables that were imputed were body mass index (BMI) (n= 4), anti-citrullinated protein antibodies (ACPA) level (n=11) as well as femoral neck BMD (n=5). Variables used for the imputation were those represented in the multivariable model in addition to lumbar spine BMD to inform the femoral neck BMD measures. Participants who had femoral neck BMD missing were those who had previously had hip replacements.

A priori variables to include in our analysis were: age, sex, race, BMI, prednisone dose, osteoporosis medication use, RA duration and ACPA positivity (4). We evaluated rheumatoid factor (RF) positivity, bDMARD and csDMARD use in univariable analyses and included those with $p<0.1$. We used multivariable linear regression to identify the independent association of low cumulative DAS28ESR with the outcome of femoral neck BMD. While we account for varying observational time by dividing the cumulative disease activity exposure by time in the study, there was a wide range of variability in the number of clinic visits per year of exposure, with some participants having relatively few clinic visits of the course of their observation time, while others, with similar observation times had a greater number of visits. As those with a greater number of visits per unit of observation time represented more precise data, we chose apply weights to the model based on number of visit. Because osteoporosis medication use can both increase BMD as well as be associated with lower BMD thereby introducing potential confounding by indication, we performed a subanalysis restricted to those not exposed to osteoporosis medications.

Sensitivity analyses:

1. To understand if our findings were similar across disease activity measures, we substituted low clinical disease activity index (CDAI) (<10) into the multivariable model as our primary disease activity predictor.
2. To evaluate whether there are site-specific associations between low cumulative disease activity and BMD, we performed additional analyses using lumbar spine BMD and total hip BMD as outcome measures using both DAS28ESR and CDAI.

Statistical significance was defined as a p-value <0.05. Statistical analyses were conducted using Stata, version 16.0 (StataCorp, College Station, TX).

Ethical Approval:

The study was approved by the UCSF Institutional Review Board, and all participants provided written informed consent.

Results:

The cohort was on average 62.4 ± 10.2 years old (age range 24–91 years) at the time of BMD measurement (Table 1). Ages were overall similar in each group. The cohort was mostly female (N=142, 88%) and the low disease activity group had a lower proportion of females than the moderate/high disease activity group (79% vs 91%). The majority of participants identified as being Hispanic/Latino (N=73, 45%), followed by Asian (N=59, 37%) and Other (N=29, 18%). The low disease activity group had a lower proportion of Hispanic/Latino participants (31% vs. 50%). RA duration was on average 10.5 ± 7.3 years, 88% (N=139) of participants were RF positive and 83% (N=125) were ACPA positive. BMI was lower in the low disease activity group (27.0 ± 4.8 vs. 28.7 ± 6.0). The low disease activity group had less prednisone exposure than the moderate/high disease activity group (2.0 ± 2.2 vs. 4.3 ± 3.9). Almost all (98%, N=157) participants were exposed to csDMARDs, and 63% (N=101) were exposed to bDMARDs throughout the observation period. Those in the low disease activity group had less bDMARD exposure overall (51% vs. 67%) and a slightly lower proportion of visits with bDMARD use when compared to the moderate/high disease activity group (33.7 ± 40.7 vs. 36.4 ± 36.0). The participants had on average 16.8 ± 10.9 study visits and were followed on average 6.4 ± 3.4 years, which were similar between groups. Time between last observation and the DXA was 0.7 ± 1.2 years. BMD T-scores were higher in the low disease activity group compared to the moderate/high disease activity group.

Univariable analyses demonstrated that bDMARD use had a significant association with femoral neck BMD (β=0.073, p=0.022) whereas csDMARD use and RF did not (β=0.018, p=0.724; β=0.001, p=0.989, respectively) (Table 2). Of our a priori variables to include in our multivariable model, ACPA positivity was the only variable that was not statistically significantly associated with femoral neck BMD (β=−0.024, p=0.466).

In the multivariable model, low cumulative disease activity was significantly associated with higher femoral neck BMD when compared to moderate/high disease activity group (β= 0.071 [95%CI: 0.021 to 0.122], p=0.020) (Table 3). Factors commonly associated with BMD, such as age and BMI, were highly statistically significant in this model (β= −0.005 [95%CI: −0.007 to −0.003], p<0.001; β = 0.005 [95%CI: 0.001 to 0.010], p=0.011, respectively). Hispanic/Latino and Asian participants both had significantly decreased femoral neck BMD compared to the Other group (β = −0.100 [95%CI: −0.162 to −0.039], p=0.002; β = −0.088 [95%CI: −0.155 to −0.021, p=0.010, respectively). Higher proportion of visits using biologic medications was associated with a significantly higher femoral neck BMD (β =0.076 [95%CI: 0.017 to 0.135], p=0.012). Results were similar when the multivariable model was performed on our original dataset without imputation (N=145).

Sensitivity analysis:

The overall relationship between low cumulative DAS28ESR and femoral neck BMD was similar in the analysis restricted to those not exposed to osteoporosis medications (n=68), but was not statistically significant (β= 0.043 [95%CI: −0.028 to 0.113], p=0.228) (data not shown).

Secondary analyses:

1. Low cumulative CDAI was independently associated with higher femoral neck BMD when it was substituted for DAS28ESR in multivariable model β= 0.051 [95%CI: 0.005 to 0.098], p=0.032 (Table 4).
2. Both low cumulative DAS28ESR and CDAI had positive associations with total hip BMD (β= 0.071 [95%CI: 0.021 to 0.122], p=0.006 and β= 0.085 [95%CI: 0.038 to 0.132], p=0.001, respectively). Relationships between both disease activity measures and lumbar spine BMD were not statistically significant.

Discussion:

In this study we found that low cumulative disease activity as measured by DAS28ESR was associated with higher femoral neck BMD, independent of traditional osteoporosis risk factors. We also found similar results when evaluating cumulative low CDAI and other BMD sites.

Our study adds to the body of literature aimed at identifying RA-specific risk factors for low BMD and does so in racial/ethnic groups traditionally under-studied in both osteoporosis and RA-related research. Prior studies of BMD in RA have evaluated baseline disease activity measures, ESR as a surrogate, or have used disease activity measures not currently recommended by the ACR(14) with varying results (8–13). Disease severity is often represented by joint damage and patient functional status,(8–10,12,24) but those are distinct concepts from active RA disease and associated inflammation. We believe our method for calculating cumulative disease activity, via the trapezoidal AUC method, provides a more accurate quantification of cumulative RA disease activity than methods used in prior studies such as mean disease activity or traditional AUC (23). We are aware of two other studies which the traditional, rectangular, AUC method with results similar to our study (3,20). In one, cumulative disease activity by rectangular AUC was associated with increased clinical FRAX score but not BMD-adjusted FRAX (the authors did not have BMD measures on participants) (3). In the other, the authors found increased disease activity by rectangular AUC to be associated with BMD loss over a short time span (1 year) (20). A recent study used propensity score matching between RA patients who were in remission versus those with active disease in the 6 months prior to measuring BMD and found that BMD was higher in those in remission (25). Although that study only evaluated disease activity over a period of 6 months prior to DXA, it further supports our findings. Importantly, a recent study evaluating mean disease activity over 3 years found more BMD loss in those with high disease activity compared to those with low disease activity (17). These data, along with our current findings, support that low cumulative RA disease activity over short and long time periods is associated with higher BMD and less BMD loss.

Our study had unique features which added to its novelty. We evaluated two modern measures of RA disease activity, DAS28ESR and CDAI, as well as multiple BMD sites. Additionally, this study was performed using data from a unique RA cohort comprised mostly of Latinx and Asian participants with long observational time. As expected, we found similar trends when studying cumulative low disease activity as measured by

DAS28ESR and CDAI at each BMD site. The association with disease activity and lumbar spine BMD, however, did not reach statistical significance, likely due to increased degenerative changes affecting BMD at this site. Importantly, well-established factors associated with BMD, age and BMI, remained highly significant in all models, which supports the quality of our data. The most unique feature of our study was the ability to evaluate these associations in a population traditionally underrepresented in RA research.

The observational nature of our study does pose limitations. First, although our study evaluated many years of data, predictor variables were collapsed over time into summary measures (e.g., AUCs, %use). While all predictors were measured prior to the DXA exam, we do not know the timing or rate of BMD loss may have been present prior to BMD assessment. Thus, we can only comment on associations rather than causation. Our cohort was an observational cohort and is subject to missing data, periods of loss to follow up and unmeasured confounders. To address missing data, we used multiple imputation with chained equations. We were limited by the size of the cohort and could not perform sex-stratified analyses. Although we included participants of all ages, DXAs were ordered based on NOF guidelines recommending DXA screening at age 50 (22) as well as by clinical suspicion if the participant had additional risk factors (e.g. chronic prednisone use). The age range represented was broad, yet the majority of study subjects were older which limits the generalizability of our findings to older people with RA. Lastly, a large percentage of the UCSF RA cohort was not included in this analysis which was mostly due to lack of DXA examinations. DXAs were not completed either because of low clinical suspicion or due to structural barriers. The safety-net hospital did not have a DXA machine, therefore participants had to travel to another site for BMD measurement. Additionally, although language assistance was provided for non-English speaking participants, this likely added an additional barrier to DXA acquisition. These limitations are balanced by the strengths of this study, which include a long period of observation with detailed measures from a US RA cohort comprised of minority groups traditionally underrepresented in RA research.

Conclusions:

We found that low cumulative disease activity was associated with increased femoral neck BMD. These data add to the evidence that supports individualized risk stratification for osteoporosis screening and treatment in RA and suggests that incorporation of cumulative disease estimates may add value to these models. Importantly, our findings further highlight the importance ACR’s recommendation to treat to target of low disease activity in RA to decrease osteoporosis risk (26). We believe our data, along with prior studies, may be used to inform future RA practice guidelines in which treatment recommendations focus not only on decreasing RA disease burden but also on the prevention of important RA comorbidities such as cardiovascular disease (27), cancer and osteoporosis.

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Data sharing statement:

The data underlying this article will be shared on reasonable request to the corresponding author.

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Highlights:

- Low cumulative disease activity was associated with higher BMD, independent of traditional osteoporosis risk factors.
- Models evaluating all central BMD sites and substituting CDAI for DAS28ESR yielded similar results.
- Our findings highlight the importance of treat to target in RA to decrease osteoporosis risk.

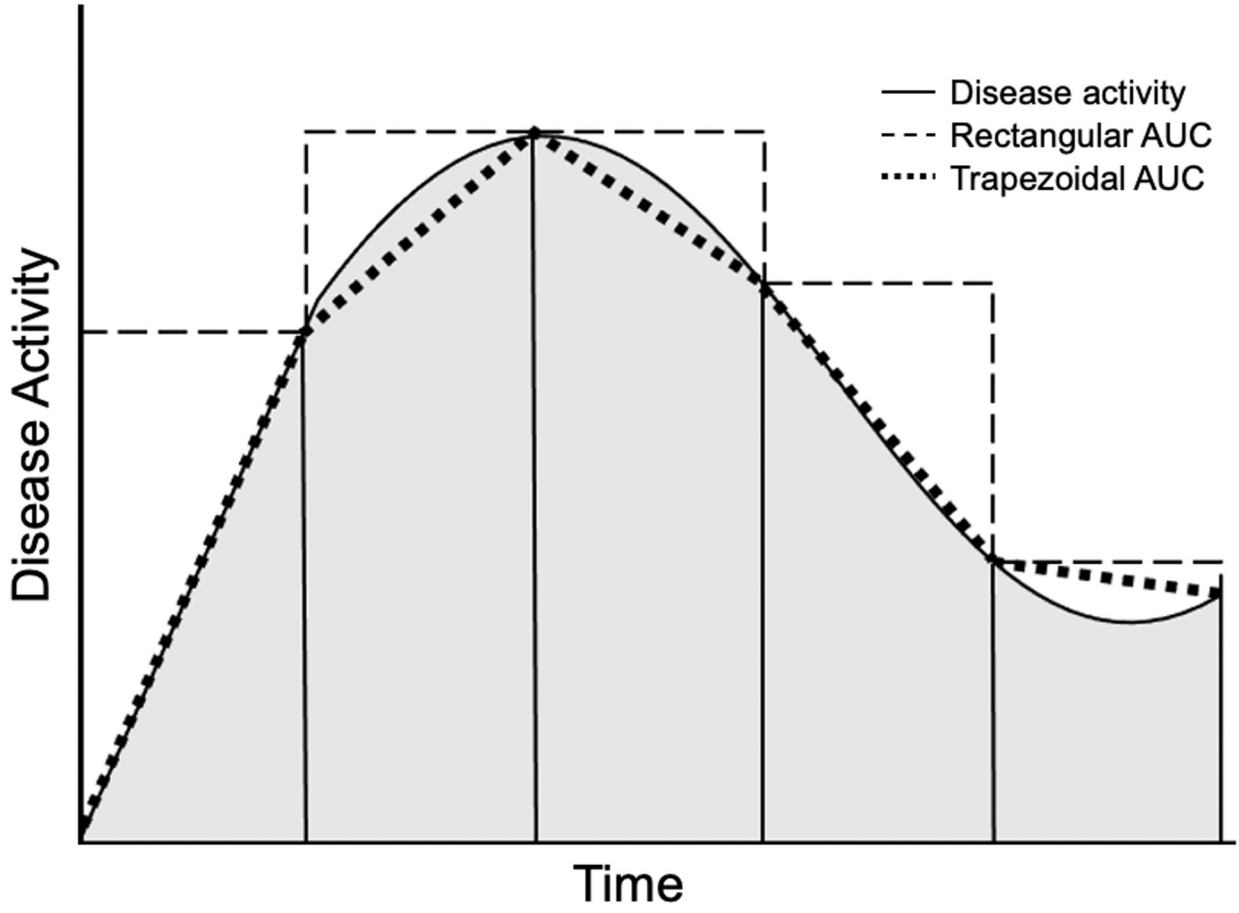

Figure 1.

Image showing an example of the trapezoidal area under the curve (AUC) method which was used to calculate disease activity as well as prednisone exposure. Trapezoidal AUC better represents the true AUC whereas rectangular AUC is prone to overestimation (23).

Table 1.

Clinical and demographic characteristics of the cohort by disease activity group as measured by DAS28ESR category: mean ± standard deviation or frequency (%).

		DAS28ESR Disease Activity Category[a,b]	
	Whole Cohort	**Low**	**Moderate/High**
Number of	161 (100%)	39 (24%)	122 (75%)
Age at DXA (years)	62.4 ± 10.2	61.8 ± 10.2	62.6 ± 10.2
Female	142 (88%)	31 (79%)	111 (91%)
Race/Ethnicity			
Hispanic/Latino	73 (45%)	12 (31%)	61 (50%)
Asian	59 (37%)	15 (38%)	44 (36%)
Other	29 (18%)	12 (31%)	17 (14%)
RA duration (years)	10.5 ± 7.3	9.6 ± 7.6	10.8 ± 7.2
RF positive	139 (88%)	35 (90%)	104 (87%)
ACPA positive	125 (83%)	32 (84%)	93 (83%)
BMI (kg/m^2)	28.3 ± 5.8	27.0 ± 4.8	28.7 ± 6.0
Prednisone (mg/day)[b]	3.7 ± 3.6	2.0 ± 2.2	4.3 ± 3.9
csDMARD ever	157 (98%)	39 (100%)	118 (97%)
csDMARD use[c]	82.8 ± 23.8	86.7 ± 20.0	0.8 ± 0.2
bDMARD ever	101 (63%)	20 (51%)	81 (67%)
bDMARD use[c]	35.8 ± 37.1	33.7 ± 40.7	36.4 ± 36.0
OP medication use (ever)	93 (58%)	16 (41%)	77 (63%)
Number of Study visits	16.8 ± 10.9	16.1 ± 12.0	17.1 ± 10.6
Years of observation	6.4 ± 3.4	6.1 ± 3.4	6.6 ± 3.4
Years from last observation to DXA	0.7 ± 1.2	0.7 ± 1.3	0.7 ± 1.1
Femoral neck BMD (g/cm^2)	0.741 ± 0.149	0.778 ± 0.162	0.728 ± 0.144
Femoral neck T-Score	−1.0 ± 1.4	−0.7 ± 1.5	−1.1 ± 1.3
Total hip T-Score	−0.6 ± 1.3	−0.3 ± 1.3	−0.7 ± 1.3
Lumbar spine T-Score	−0.9 ± 1.6	−0.5 ± 1.6	−1.1 ± 1.6
DAS28ESR[b]	4.1 ± 1.1	2.7 ± 0.4	4.5 ± 0.9
CDAI[b]	15.2 ± 8.8	7.0 ± 3.5	17.9 ± 8.4

-DAS28ESR: Disease activity score 28-joints with erythrocyte sedimentation rate; DXA: dual x-ray absorptiometry; RA: rheumatoid arthritis; BMI: body mass index; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; bDMARD: biologic DMARD; OP: osteoporosis; BMD: bone mineral density; CDAI: clinical disease activity index.

[a]-Low DAS28ESR ≤3.2, moderate/high DAS28ESR >3.2.

[b]-Calculated using trapezoidal area under the curve/observation time.

[c]-Calculated as proportion (%) of visits where participant was taking csDMARDs or bDMARDs.

Table 2.

Associations between clinical variables and the primary outcome femoral neck BMD (g/cm^2) as determined by univariable linear regression.

	β	95% CI	p-value
Low disease activity[a,b]	0.050	−0.003 to 0.104	0.066
Age at time of DXA (years)	−0.006	−0.008 to −0.004	<0.0001
Female	−0.045	−0.117 to 0.026	0.212
Race/Ethnicity			
Hispanic/Latino	−0.053	−0.116 to 0.010	0.097
Asian	−0.099	−0.164 to −0.033	0.003
Other	ref	--	--
RA disease duration	−0.002	−0.005 to 0.002	0.321
BMI	0.009	0.006 to 0.013	<0.0001
csDMARD use[c]	0.018	−0.081 to 0.116	0.724
bDMARD use[c]	0.073	0.011 to 0.135	0.022
Prednisone (mg/day)[b]	0.004	−0.003 to 0.010	0.250
RF positive	−0.001	−0.073 to 0.072	0.989
ACPA positive	−0.024	−0.087 to 0.040	0.466
OP medication use (ever)	−0.047	−0.094 to −0.001	0.049
Number of visits	0.001	−0.001 to 0.002	0.379

-DAS28ESR: Disease activity score 28-joints with erythrocyte sedimentation rate; DXA: dual x-ray absorptiometry; RA: rheumatoid arthritis; BMI: body mass index; csDMARD: conventional synthetic disease modifying antirheumatic drug; bDMARD: biologic disease modifying anti-rheumatic drug; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide; OP: osteoporosis.

-p-value:

*<0.1,

**<0.05,

***<0.001.

[a]-Low DAS28ESR ≤3.2 vs. moderate/high DAS28ESR >3.2.

[b]-Cumulative values calculated using trapezoidal area under the curve/observation time.

[c]-Calculated as proportion (%) of visits where participant was taking bDMARDs or csDMARDs.

Table 3.

Multivariable linear regression model evaluating the association between low cumulative RA disease activity category as measured by DAS28ESR and femoral neck bone mineral density (gm/cm^2) controlling for important demographic and clinical variables. The model was weighted by number of study visits.

	β	95% CI	p-value
Low disease activity[a,b]	0.071	0.021 to 0.122	0.020
Age at time of DXA (years)	−0.005	−0.007 to −0.003	<0.0001
Female	−0.021	−0.084 to 0.042	0.502
Race/Ethnicity			
Hispanic/Latino	−0.100	−0.162 to −0.039	0.002
Asian	−0.088	−0.155 to −0.021	0.010
Other	ref	--	--
RA duration (years)	−0.001	−0.004 to 0.002	0.533
BMI	0.005	0.001 to 0.010	0.016
bMDARD use[c]	0.076	0.017 to 0.135	0.012
Prednisone (mg/day)[b]	0.004	−0.005 to 0.012	0.381
ACPA positive	−0.013	−0.076 to 0.050	0.680
OP medication use (ever)	−0.002	−0.056 to 0.051	0.931

-DAS28ESR: Disease activity score 28-joints with erythrocyte sedimentation rate; DXA: dual x-ray absorptiometry; RA: rheumatoid arthritis; BMI: body mass index; bDMARD: biologic disease modifying anti-rheumatic drug; ACPA: anti-cyclic citrullinated peptide; OP: osteoporosis.

[a]-Low DAS28ESR ≤3.2 vs. moderate/high DAS28ESR >3.2.

[b]-Cumulative values calculated using trapezoidal area under the curve/observation time.

[c]-Calculated as proportion (%) of visits where participant was taking bDMARDs.

Table 4.

Multivariable linear regression models evaluating the relationship of disease activity, represented by low DAS28ESR and CDAI at three sites: femoral neck, total hip and lumbar spine. All models control for the same variables in our primary model and were similarly weighted by number of study visits.

	Low DAS28ESR [a,b]			Low CDAI [a,b]		
	β	95% CI	p-value	β	95% CI	p-value
Femoral Neck[c]	0.071	0.021 to 0.122	0.020	0.051	0.005 to 0.098	0.032
Total Hip[c]	0.071	0.021 to 0.122	0.006	0.085	0.038 to 0.132	0.001
Lumbar Spine[c]	0.060	−0.004 to 0.124	0.067	0.057	−0.005 to 0.118	0.069

-DAS28ESR: Disease activity score 28-joints with erythrocyte sedimentation rate; CDAI: clinical disease activity index; DXA: dual x-ray absorptiometry; RA: rheumatoid arthritis; anti-cyclic citrullinated peptide; bDMARD: biologic disease modifying anti-rheumatic drug; OP: osteoporosis; BMI: body mass index.

a-Low DAS28ESR DAS28ESR ≤3.2 vs. moderate/high DAS28ESR >3.2.; Low CDAI <10 vs. high/moderate ≥10.

b-Cumulative values calculated using trapezoidal area under the curve/observation time.

c-Controlled for: age at DXA, female sex, race/ethnicity, RA duration, BMI, bDMARD use, Prednisone dose, ACPA positivity and OP medication use.