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Sex differences in frailty and its association with low bone mineral density in rheumatoid arthritis

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ABSTRACT

Objectives: Frailty in the general population is associated with poor health outcomes including low bone mass and osteoporotic fracture. The relationship between frailty and low bone mineral density (BMD) in rheumatoid arthritis (RA) is unknown. This study examined associations between frailty and BMD in RA, controlling for established osteoporosis risk factors.

Methods: We performed a cross-sectional analysis of a longitudinal RA cohort (n = 138; 117 female, 21 male). Participants fulfilled ACR RA classification criteria. Frailty was evaluated using the Fried Index, categorizing each participant as robust, pre-frail or frail. To identify independent predictors of BMD, we performed a multivariable linear regression analysis. Because risk factors for low BMD differ between sexes, we performed additional sex-stratified multivariable analyses.

Results: Mean age and disease duration were 58.0 ± 10.8 and 19 ± 10.9 years, respectively. The majority of participants were categorized as pre-frail (70%) or frail (10%). Females had higher rates of frailty than males. In the whole cohort, both pre-frail and frail had independent negative associations with BMD (β = −0.074 and −0.092 respectively, p < 0.05). In sex-stratified analyses, frailty did not have a significant association with BMD in females, but had a strong independent negative association in males (β = −0.247, p = 0.001).

Conclusion: Frailty was associated with BMD in patients with RA. Females had higher rates of frailty than males, yet frailty was independently associated with BMD in males but not in females. Frailty appears to be an important factor associated with low BMD; sex may influence this relationship in RA.

1. Introduction

Frailty, defined as "an excess of vulnerability to stressors" with a lack of resilience after a stressful event, is an important consideration in the management of patients with chronic illnesses (Walston et al., 2006). Frailty is associated with increased mortality independent of comorbid conditions (Walston et al., 2006; Fried et al., 2001). Both frailty and rheumatoid arthritis (RA) are independently associated with osteoporotic fractures, which lead to considerable morbidity and mortality (Book et al., 2009; Staa et al., 2006; Ensrud et al., 2007).

To date, few investigators have examined the rates and consequences of frailty in RA. Previous studies have found frailty was associated with higher disease activity scores and that frailty occurs both at a younger age and at a higher prevalence in RA than in non-RA geriatric cohorts (Chen et al., 2009; Salaffi et al., 2019; Andrews et al., 2017; Haider et al., 2019). Prior to this year, the association between frailty and osteoporosis in RA had been unstudied. A recent Canadian registry-based study by Li et al., found that frailty measured by a Rockwood-type patient-reported index (Rockwood et al., 2005), was associated with a hospital visit for fracture in persons with RA (Li et al., 2019). The study by Li et al. was foundational, yet it had limitations. The frailty index used was developed ad hoc, and therefore, was not validated against accepted frailty measures, and Li et al. were unable to control for bone mineral density (BMD) (Li et al., 2019). The aim of the current study was to explore the association of frailty and osteoporosis in RA further, by evaluating a cohort of RA patients for which BMD and

Abbreviations: BMD, bone mineral density; RA, rheumatoid arthritis; ACPA, anti-citrullinated protein antibody; Anti-CCP, anti-cyclic citrullinated peptide; DXA, dual x-ray absorptiometry; IPAQ, International Physical Activity Questionnaire; BMI, body mass index; FMI, fat mass index; ALMI, appendicular lean mass index; RADAI, Rheumatoid Arthritis Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; TNF, tumor necrosis factor

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Table 1
Demographic, clinical, body composition, medication and frailty variables. Values are presented for the entire cohort (n = 138) and by sex.

Variables	Whole cohort (n = 138)	Female (n = 117)	Male (N = 21)	p-Value[g]
Demographics				
Age	58.0 ± 10.8	57.3 ± 11.0	61.9 ± 9.2	0.072
White race	107 (78%)	88 (75%)	10 (90%)	0.123
Disease characteristics				
RF positive	96 (70%)	81 (69%)	15 (71%)	0.840
High positive anti-CCP[a]	76 (55%)	64 (55%)	12 (57%)	0.867
Disease duration (years)	19.0 ± 10.9	19.7 ± 11.1	15.0 ± 8.6	0.071
Current smoker	8 (5.8%)	6 (5%)	2 (10%)	0.427
RADAI score	2.6 ± 1.8	2.7 ± 1.8	2.1 ± 1.4	0.167
ESR (median, IQR)	13 (4–27)	13 (4–26)	17 (6–30)	0.348
CRP (median, IQR)	1.8 (0.7–5.0)	1.6 (0.7–4.2)	4.7 (1.8–8.4)	0.022
Body composition				
BMI (kg/m^2)	27.2 ± 6.0	27.0 ± 6.4	28.2 ± 3.7	0.423
FMI (kg/m^2)	10.8 ± 4.6	11.1 ± 4.8	9.2 ± 2.8	0.091
DXA obese[b]	72 (52%)	59 (50%)	13 (62%)	0.332
Appendicular LMI (kg/m^2)	6.4 ± 1.2	6.2 ± 1.1	7.6 ± 1.0	< 0.0001
Femoral neck BMD (g/cm^2)	0.883 ± 0.137	0.870 ± 0.126	0.951 ± 0.175	0.013
Low BMD[c]	23 (17%)	18 (15%)	5 (24%)	0.340
Very low BMD[c]	2 (1%)	0	2 (10%)	0.001
Medications				
Subjects on prednisone	44 (32%)	36 (31%)	8 (38%)	0.542
Mean dose among those reporting use (mg/day)	7.1 ± 6.1	6.8 ± 6.2	8.7 ± 5.6	0.423
TNF inhibitor	63 (46%)	32 (39%)	31 (55%)	0.251
Osteoporosis medication[d,e]	31 (27%)	28 (28%)	3 (19%)	0.450
Frailty category[f]				
Robust	27 (20%)	19 (16%)	8 (38%)	0.059
Pre-frail	97 (70%)	85 (73%)	12 (57%)	–
Frail	14 (10%)	13 (11%)	1 (5%)	–
Frailty components[f]				
Low weight	3 (2%)	3 (3%)	0 (0%)	0.458
Exhaustion	39 (28%)	37 (32%)	2 (10%)	0.038
Low gait speed	10 (8%)	10 (10%)	0 (0%)	0.136
Low grip strength	77 (59%)	66 (60%)	11 (52%)	0.516
Low physical activity	46 (33%)	41 (35%)	5 (24%)	0.315

RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibody; RADAI: rheumatoid arthritis disease activity index, ESR: erythrocyte sedimentation rate, CRP: high-sensitivity c-reactive protein, BMI: body mass index; FMI: fat mass index; DXA: dual x-ray absorptiometry; LMI: lean mass index; BMD: bone mineral density; TNF: tumor necrosis factor.

[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.

[b] DXA obese was defined using % body fat from DXA based on age, sex, and race-specific criteria.

[c] Low BMD was defined as a Z-score ≤ -1.0 and very low BMD was defined as a Z-score ≤ -2.0 at the femoral neck.

[d] Osteoporosis medications represent bisphosphonate use. One patient self-reported estrogen use, but was also taking bisphosphonates. No subjects recorded use of parathyroid hormone, raloxifene or calcitonin.

[e] n = 117. Due to differences in interview protocols, this question was not asked of all participants.

[f] Frailty category as defined by Fried Frailty Index (Fried et al., 2001) (1 point for each component. Score of 0 = robust; 1–2 = pre-frail; 3+ = frail). Low weight was based on BMI. Exhaustion was based on patient self-report. Low gait speed is based on the 4-meter walking speed test. Low grip strength is measured by hand-held dynamometer. Low physical activity was based on the International Physical Activity Questionnaire (Giles et al., 2008a).

[g] p-Value refers to the difference between female and male study subjects assessed by *t*-test for continuous variables or χ^2 test for categorical variables. Wilcoxon rank-sum test used for ESR and CRP given non-normal distribution.

body composition measures were available, using an established and validated clinical measure of frailty (Fried et al., 2001). Additionally, we evaluated if the association between frailty and BMD differed by sex. We hypothesized that frailty would have a strong association with BMD in participants with RA when controlling for other important clinical variables.

2. Methods

2.1. Subjects

Individuals in this study were participants in the Arthritis, Body Composition, and Disability (ABCD) study, a cohort developed at the University of California, San Francisco (UCSF) to study relationships between body composition and physical function in patients with RA and systemic lupus erythematosus. Data were collected between 2007 and 2009. Details of this cohort have been previously reported by Katz et al. (2012). Briefly, the patients of the ABCD cohort were recruited from two sources: (1) 101 participants were recruited from a previous cohort recruited from a random sample of rheumatologists practicing in Northern California and (2) 44 from the UCSF Rheumatology Clinic. For this study, we evaluated only those patients with rheumatologist-diagnosed RA and with a single femoral neck BMD measure. Exclusion criteria were non-English-speaking, age < 18 years and current pregnancy. Seven participants were excluded from the analysis because they did not complete the body composition assessment (including dual x-ray absorptiometry (DXA) BMD measurement). Of the remaining 138 participants, 117 (85%) were females and 21 (15%) were males.

2.2. Variables

2.2.1. Bone mineral density (BMD) and body composition

BMD and body composition were assessed in the UCSF Clinical Research Center using the Lunar Prodigy DXA system (software version 9.3). DXA has been validated as a method of assessing BMD as well as body composition and has good reproducibility (Mazess et al., 1990;

Table 2
Univariable linear regressions between variables and femoral neck bone mineral density (g/cm^2) for entire cohort and stratified by sex. Beta coefficients (β) and associated p-values are presented.

Variables	Whole cohort (N = 138)		Female (N = 117)		Male (N = 21)	
	β	p-Value	β	p-Value	β	p-Value
Basic demographics						
Age	**−0.004**	**< 0.0001**	**−0.004**	**< 0.0001**	−0.006	0.198
White race	0.000	0.991	−0.013	0.625	0.036	0.791
Female sex	**−0.080**	**0.013**	–	–	–	–
Disease characteristics						
RF positive	**−0.060**	**0.018**	**−0.062**	**0.014**	−0.058	0.508
High positive anti-CCP[a]	**−0.069**	**0.003**	**−0.063**	**0.007**	−0.108	0.169
Disease duration (years)	**−0.003**	**0.006**	**−0.002**	**0.043**	−0.007	0.114
Current smoker	0.038	0.447	0.076	0.152	−0.114	0.393
RADAI score	0.006	0.375	0.010	0.106	−0.016	0.578
ESR	0.000	0.749	0.000	0.645	0.001	0.578
CRP	−0.001	0.452	0.000	0.787	−0.004	0.162
Body composition variables						
BMI (kg/m^2)	**0.006**	**0.002**	**0.006**	**< 0.0001**	−0.008	0.446
FMI (kg/m^2)	*0.004*	*0.083*	**0.007**	**0.002**	*−0.026*	*0.061*
DXA obese[b]	0.035	0.143	**0.063**	**0.007**	−0.098	0.208
Appendicular LMI (kg/m^2)	**0.052**	**< 0.0001**	**0.045**	**< 0.0001**	**0.093**	**0.016**
Medications						
Mean prednisone dose (mg/day)	−0.003	0.261	0.000	0.913	**−0.016**	**0.020**
TNF inhibitor	−0.004	0.854	−0.003	0.909	−0.051	0.521
Osteoporosis medication[c,d]	**−0.100**	**< 0.0001**	**−0.087**	**0.001**	−0.150	0.162
Frailty category[e]						
Robust	Ref	–	Ref	–	Ref	–
Pre-frail	**−0.101**	**0.001**	−0.041	0.202	**−0.246**	**0.001**
Frail	**−0.099**	**0.025**	−0.035	0.443	**−0.295**	**0.045**

Bolded values = significant at p < 0.05 level. *Italicized values* = significant at p < 0.1 level.
RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibody; RADAI: rheumatoid arthritis disease activity index; ESR: erythrocyte sedimentation rate; CRP: high-sensitivity c-reactive protein; BMI: body mass index; FMI: fat mass index; DXA: dual x-ray absorptiometry; LMI: lean mass index; BMD: bone mineral density; TNF: tumor necrosis factor.
[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.
[b] DXA obese was defined using % body fat from DXA based on age, sex, and race-specific criteria.
[c] Osteoporosis medications represent bisphosphonate use. One patient self-reported estrogen use, but was also taking bisphosphonates. No subjects recorded use of parathyroid hormone, raloxifene or calcitonin.
[d] n = 117. Due to differences in interview protocols, this question was not asked of all participants.
[e] Frailty category as defined by Fried Frailty Index (Fried et al., 2001) (score of 0 = robust; 1–2 = pre-frail; 3+ = frail).

Table 3
Multivariable linear regression of the entire cohort on the outcome of femoral neck bone mineral density (g/cm^2) (N = 135, r^2 = 0.32).

Variables	β	95% CI	p-Value
Age	−0.003	−0.005 to −0.001	0.001
Female sex	−0.067	−0.125 to −0.008	0.027
High positive anti-CCP[a]	−0.049	−0.090 to −0.008	0.019
Disease duration (years)	−0.001	−0.003 to 0.001	0.303
BMI[b]	0.007	0.003 to 0.010	< 0.0001
Frailty[c]			
Robust	Ref	–	–
Pre-frail	−0.074	−0.129 to −0.020	0.008
Frail	−0.092	−0.177 to −0.006	0.035

All variables included in the multivariate model are shown in table.
CCP: cyclic citrullinated peptide antibody; BMI: body mass index.
[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.
[b] BMI calculated as weight (kg) divided by height (m^2).
[c] Categories based on Fried Frailty Index (Fried et al., 2001) (score of 0 = robust; 1–2 = pre-frail; 3+ = frail).

Visser et al., 2003). The root-mean-square coefficient of variation for the Lunar Prodigy DXA system is 0.77% for BMD, 2.98% for total fat and 1.42% for lean mass (Knapp et al., 2015). Bone mass is reported regionally on whole body DXA and is therefore not suitable for the study of osteoporosis. This study obtained a single site BMD at the hip and used BMD at the femoral neck as the primary outcome measure (g/cm^2). To describe the cohort, we created a dichotomous variables low BMD and very low BMD that identified participants with femoral neck Z-score ≤ -1.0 and ≤ -2.0, respectively. We used Z-scores, rather than T-scores, to describe our cohort given the wide age range of the participants in our study (25–87 years old).

Weight was measured with subjects wearing light indoor clothing and no shoes. Height was measured with a wall-mounted stadiometer. BMI (body mass index) was calculated as weight (kg) divided by height (m^2). DXA has previously been used to study body composition in RA (Katz et al., 2012; Giles et al., 2008a; Giles et al., 2008b) and yields data on total percent body fat as well as total and segmented fat and lean mass. Obesity was defined using a method that linked percent fat from DXA to the National Institutes of Health BMI obesity criterion (BMI $\geq$30 kg/m^2) by sex, age, and race (Gallagher et al., 2000). This definition has been previously used in RA and is thought to represent a conservative measure of obesity (Katz et al., 2012). Fat mass (FMI) and appendicular lean mass (ALMI) indices were calculated as kg/m^2.

2.2.2. Frailty measures

Frailty was measured by the Fried index (Fried et al., 2001), which is based on 5 different domains (van Kan et al., 2008). The domains are low weight, exhaustion, weakness, low speed and low physical activity. For our study we used: (1) Low weight (based on a BMI < 18.5 kg/m^2) (Bandeen-Roche et al., 2006); and (2) Do you feel exhausted? (0 = rarely or a little of the time, 1 = a moderate amount of time or

Table 4
Multivariable linear regression on the outcome of femoral neck bone mineral density (g/cm^2) by sex. R^2 for female model 0.29 and for males 0.66.

Variables	Females (N = 114)			Males (N = 21)		
	β	95% CI	p-Value	β	95% CI	p-Value
Age	−0.004	−0.006 to −0.002	< 0.0001	−0.002	−0.008 to 0.005	0.620
High positive anti-CCP[a]	−0.050	−0.093 to −0.007	0.022	−0.010	−0.237 to 0.037	0.141
Disease duration (years)	−0.001	−0.003 to 0.001	0.541	−0.003	−0.011 to 0.006	0.512
BMI[b]	0.006	0.003 to 0.010	< 0.0001	−0.001	−0.017 to 0.015	0.908
Pre-frail and frail[c]	−0.023	−0.083 to 0.037	0.449	−0.247	−0.366 to −0.127	0.001

All variables included in the multivariate model are shown in table.
CCP: cyclic citrullinated peptide antibody; BMI: body mass index.
[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.
[b] BMI calculated as weight (kg) divided by height (m^2).
[c] Due to the smaller numbers of individuals analyzed in the sex-stratified analyses, pre-frail and frail categories (as defined by Fried Frailty Index (Fried et al., 2001): 0 = robust; 1–2 = pre-frail; 3+ = frail) were combined.

most of the time); (3) Hand grip strength (as measured by a hand-held dynamometer (Haider et al., 2019)); (4) 4-meter walking speed test; and (5) Physical activity as measured by the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). Grip strength was classified as normal or low, according to sex and BMI-based cutoffs established by Fried et al. Fried et al., 2001. Walking speed was classified as normal or slow, based on gender and height-based criteria (Fried et al., 2001). Lastly, the IPAQ was categorized as normal or low according to sex-based cutoffs (Craig et al., 2003). For each frailty measure, if the participant met the cutoff, they were given one point, and points were combined to tally the number of frailty criteria present (0 criteria present = robust, 1–2 = prefrail and 3–5 = frail).

2.2.3. RA disease characteristics and medications

RA disease duration (in years), smoking status, and Rheumatoid Arthritis Disease Activity Index (RADAI) were obtained by self-report (Anderson et al., 2011). Blood samples were collected during the study visit. Erythrocyte sedimentation rate (ESR), high sensitivity c-reactive protein (CRP), rheumatoid factor (RF) and anti-CCP levels were measured at a single commercial laboratory. RF was determined to be positive if > 10 IU/mL. We used the European League Against Rheumatism/American College of Rheumatology 2010 classification criteria definition of high-positive anti-CCP which is defined as three times the upper limit of normal (Aletaha et al., 2010). Using this criterion, the cutoff for high anti-CCP positivity in our study was 60 units. In order to minimize the heterogeneity of the high anti-CCP group, participants who fell within the low-to-intermediate anti-CCP positive group (n = 10) were included with those who were anti-CCP negative. Almost 80% of study participants were concordant in their RF and anti-CCP status.

Use and dosage of prednisone and tumor necrosis factor (TNF) inhibitors were queried. Current osteoporosis medication and calcium and vitamin D use were determined by self-report. Information on past RA and osteoporosis medication use was not collected.

2.2.4. Other

Age, race, and smoking status were self-reported.

2.3. Statistical analyses

Chi-square and *t*-test analyses were used to detect sex differences in participant characteristics. Linear regression analyses were used to determine univariable associations between predictors and femoral neck BMD. To identify independent predictors of BMD, we performed multivariable linear regression analyses that included variables significant in the univariable analyses of the total sample at $p < 0.10$, with the three exceptions detailed below (Table 2).

(1) Osteoporosis medications were not included in the multivariable analyses due to the inverse association with BMD suggesting confounding by indication.
(2) To avoid multi-collinearity, given high concordance between RF and high anti-CCP positivity, we used anti-CCP status in multivariable models due to its stronger univariable association with femoral neck BMD.
(3) Because DXA based body composition measures are not routinely available clinically and because ALMI highly correlated with the strength measure in the frailty index, we chose to use BMI in our primary model (rather than ALMI and FMI).

2.3.1. Sex stratified analysis

Because many risk factors for low BMD differ between males and females, univariable and multivariable analyses were performed on the entire study population and then stratified by sex. Due to lower numbers of participants for analysis in the sex-stratified models, frailty categories (pre-frail and frail) were combined to create a dichotomous predictor for use in the multivariable models. Statistical analyses were conducted using Stata, version 15.1 (StataCorp, College Station, TX).

2.3.2. Sensitivity analyses

(1) To evaluate if frailty maintained its relationship with femoral neck BMD when controlling for specific body composition measures, we replaced BMI with ALMI and FMI.
(2) In the primary analysis, we did not add osteoporosis medication to the model due to its negative association with femoral neck BMD (suggesting confounding by indication). In the second sensitivity analyses, we performed a multivariable analysis restricted to subjects reporting no OP medication use.
(3) Lastly, to understand which frailty component best explained the relationship with BMD, a multivariable model was performed substituting the individual frailty components for the categorical frailty variable.

2.3.3. Frailty group characteristics

A descriptive table of demographic, clinical, body composition and medication variables was made to better understand the characteristics of the frailty groups (Table 6). Statistical testing was performed to determine differences between the 3 frailty categories. One-way ANOVA was performed for all variables except for tests of medians where Kruskal-Wallis test was performed.

2.4. Ethical approval

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

Table 5
Sensitivity analyses. Multivariable linear regression models with the outcome of femoral neck bone mineral density (g/cm^2).

Variables	β	95% CI	p-Value
Sensitivity analysis 1: entire cohort, substituting appendicular lean mass index (ALMI) and fat mass index (FMI) for body mass index (BMI). N = 135, R^2 = 0.36.			
Age	−0.003	−0.005 to −0.001	0.002
Female sex	−0.028	−0.095 to 0.040	0.419
High positive anti-CCP[a]	−0.048	−0.089 to −0.008	0.019
Disease duration (years)	−0.001	−0.003 to 0.001	0.556
Appendicular LMI[b]	0.040	0.016 to 0.063	0.001
FMI[b]	0.002	−0.004 to 0.007	0.602
Frailty[c]			
Robust	Ref	–	–
Pre-frail	−0.056	0.111 to −0.002	0.043
Frail	−0.051	−0.139 to 0.037	0.252
Sensitivity analysis 2: entire cohort, restricted to subjects who did not report osteoporosis medication use. N = 86, R^2 = 0.29.			
Age	−0.002	−0.005 to 0.001	0.095
Female sex	−0.097	−0.179 to −0.015	0.021
High positive anti-CCP[a]	−0.044	−0.097 to 0.009	0.106
Disease duration (years)	−0.002	−0.004 to 0.001	0.239
BMI[b]	0.006	0.002 to 0.011	0.007
Frailty[c]			
Robust	Ref	–	–
Pre-frail	−0.044	−0.111 to 0.023	0.194
Frail	−0.111	−0.250 to 0.028	0.115
Sensitivity analysis 3: entire cohort, substituting individual Fried frailty subcomponents for the composite frailty variable. N = 128, R^2 = 0.28.			
Age	−0.003	−0.006 to −0.001	0.002
Female sex	−0.071	−0.131 to −0.011	0.021
High positive anti-CCP[a]	−0.058	−0.103 to −0.013	0.011
Disease duration (years)	−0.001	−0.003 to 0.001	0.261
BMI[b]	0.007	0.003 to 0.011	0.001
Frailty components[d]			
Low weight	0.113	−0.032 to 0.257	0.125
Exhaustion	−0.042	−0.098 to 0.014	0.144
Low gait speed	0.044	−0.045 to 0.133	0.133
Low grip strength	−0.056	−0.102 to −0.010	0.017
Low physical activity	−0.027	−0.076 to 0.022	0.283

All variables included in the multivariate models are shown in table.
CCP: cyclic citrullinated peptide antibody; BMI: body mass index; DXA: dual x-ray absorptiometry; LMI: lean mass index; FMI: fat mass index.

[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.

[b] Appendicular LMI, FMI, and BMI (kg/m^2).

[c] Categories based on Fried Frailty Index (Fried et al., 2001) (score of 0 = robust; 1–2 = pre-frail; 3+ = frail).

[d] Low weight was based on BMI. Exhaustion was based on patient self-report. Low gait speed is based on the 4-meter walking speed test. Low grip strength is measured by hand-held dynamometer. Low physical activity was based on the International Physical Activity Questionnaire (Giles et al., 2008a).

3. Results

3.1. Cohort characteristics and primary analysis

The cohort was comprised of 138 participants; 117 were female (85%). The average age was 58 ± 10.8 years and 78% were white (Table 1). Subjects had mean RA disease duration of 19 ± 10.9 years, 70% were RF positive and 55% were high anti-CCP positive. Approximately 17% had low femoral neck BMD defined as Z-score ≤ −1.0 and 27% of study participants reported taking osteoporosis medications. One individual self-reported estrogen use and also reported taking a bisphosphonate. No subjects reported use of parathyroid hormone (1–34), raloxifene or calcitonin.

Disease and medication characteristics were similar between males and females (Table 1), with the exception that males had a significantly higher median CRP value than females. Males also had statistically significantly higher ALMI and BMD than females. Rates of obesity as defined by DXA total fat were high in both groups. Females had higher rates of pre-frailty and frailty when compared to males, however, the differences were not statistically significant (p = 0.059). Low grip strength, inactivity and exhaustion represented the most common frailty components (Table 1). The frailty components were similar among males and females except for exhaustion, which was more common in females (32% vs. 10%, p = 0.038).

Univariable associations with BMD determined that age, female sex, RF positivity, high anti-CCP positivity and longer disease duration had significant negative associations with BMD (p < 0.05) (Table 2). BMI and ALMI were positively associated with BMD (p < 0.05). Pre-frailty and frailty also had strong significant negative associations with BMD. Sex differences were noted in the univariable associations with BMD. Notably, pre-frailty and frailty had strong negative associations with femoral neck BMD in males (β = −0.246 and −0.295, p < 0.05), but not in females (β = −0.041 and −0.035, p = 0.202 and 0.443).

Age, female sex, high anti-CCP positivity, disease duration, BMI and the frailty categories met the pre-specified inclusion criterion from univariable analyses and were included in the primary multivariable linear regression model. Greater age, female sex, and high-positive anti-CCP titers were significantly and independently associated with lower BMD (Table 3). BMI had a positive association with femoral neck BMD. The pre-frail and frail categories had the strongest negative associations with BMD (β = −0.074 and − 0.092 respectively, p < 0.05).

Results from sex-specific multivariable linear regressions analyses are shown in Table 4. In females, age and high anti-CCP positivity maintained negative associations with BMD, and BMI maintained its significant positive association with BMD. The composite frailty variable was not significant in the model restricted to females, yet it did maintain its negative beta-coefficient. The composite frailty variable was the sole statistically significant variable in the male model with the strongest point estimate of all variables of all models (β = −0.247, p = 0.001).

3.2. Sensitivity analyses (Table 5)

(1) Body composition measures (ALMI and FMI) substituted for BMI: prefrail and frail categories continued to have negative associations with femoral neck BMD. The relationships were attenuated with slightly lower beta-coefficients, and only pre-frailty achieved statistical significance (β = −0.056, p < 0.05).
(2) Restricted to OP-medication naïve participants: beta coefficients were similar to the primary model for all variables, but the frailty variables did not reach statistical significance.
(3) Evaluating individual frailty components independently: Of the frailty components, only low grip strength had an independent negative association with lower femoral neck BMD (β = −0.056, p < 0.05).

3.3. Characteristics of the three frailty groups (Table 6)

Important differences between the three frailty groups (robust, pre-frail and frail) were found (Table 6). Notably, the self-reported disease activity (RADAI score) was higher in the frail group, as were levels of inflammation, as measured by ESR and CRP. There were also significant body composition differences between the three groups, with higher BMI, FMI and obesity in the pre-frail and frail groups. As expected, the

Table 6
Demographic, clinical, body composition and medication variables stratified by frailty category based on the Fried Frailty Index (Fried et al., 2001).

Variables	Robust (n = 27)[f]	Pre-frail (n = 97)[f]	Frail (n = 14)[f]	p-Value[g]
Demographics				
Age	54.3 ± 11.5	58.8 ± 10.8	59.1 ± 9.2	0.143
Female sex	19 (70%)	85 (88%)	13 (93%)	0.059
White race	23 (85%)	76 (78%)	8 (57%)	0.117
Disease characteristics				
RF positive	16 (59%)	70 (72%)	10 (71%)	0.430
High positive anti-CCP[a]	10 (37%)	57 (59%)	9 (64%)	0.093
Disease duration (years)	15.7 ± 9.0	20.0 ± 11.4	18.5 ± 9.7	0.186
Current smoker	1 (4%)	6 (6%)	1 (7%)	0.865
RADAI score	1.6 ± 1.2	2.7 ± 1.7	4.0 ± 1.7	< 0.001
ESR (median, IQR)	9.0 (4–15)	14.5 (4–28)	20.5 (13 − 32)	0.029
CRP (median, IQR)	1.2 (0.6–3.1)	1.8 (0.7–4.9)	4.8 (1.6–12.3)	0.035
Body composition				
BMI (kg/m^2)	24.9 ± 3.3	27.2 ± 5.8	31.6 ± 9.0	0.003
FMI (kg/m^2)	8.3 ± 2.1	10.9 ± 4.4	14.7 ± 6.0	< 0.0001
DXA obese[b]	8 (30%)	61 (63%)	12 (86%)	0.001
Appendicular LMI (kg/m^2)	6.8 ± 1.2	6.3 ± 1.1	6.4 ± 1.7	0.260
Femoral neck BMD (g/cm^2)	0.964 ± 0.163	0.863 ± 0.123	0.865 ± 0.104	0.002
Low BMD[c]	3 (11%)	18 (19%)	2 (14%)	0.623
Very low BMD[c]	0	2 (2%)	0	0.804
Medications				
Subjects on prednisone	4 (15%)	33 (34%)	7 (50%)	0.051
Mean dose among those reporting use (mg/day)	3.4 ± 1.4	6.5 ± 4.4	11.9 ± 11.1	0.040
TNF inhibitor	13 (48%)	45 (46%)	5 (36%)	0.724
Osteoporosis medication[d,e]	3 (12%)	24 (29%)	4 (50%)	0.076

RF: rheumatoid factor; CCP: cyclic citrullinated peptide antibody; RADAI: rheumatoid arthritis disease activity index; ESR: erythrocyte sedimentation rate; CRP: high-sensitivity c-reactive protein; BMI: body mass index; FMI: fat mass index; DXA: dual x-ray absorptiometry; LMI: lean mass index; BMD: bone mineral density; TNF: tumor necrosis factor.

[a] High positive anti-CCP defined as level three times the upper limit of normal (> 60 units) based on the 2010 EULAR/ACR RA classification criteria (Aletaha et al., 2010). This threshold was used to minimize heterogeneity of this group.

[b] DXA obese was defined using % body fat from DXA based on age, sex, and race-specific criteria.

[c] Low BMD was defined as a Z-score ≤ −1.0 and very low BMD was defined as a Z-score ≤ −2.0 at the femoral neck.

[d] Osteoporosis medications represent bisphosphonate use. One patient self-reported estrogen use, but was also taking bisphosphonates. No subjects recorded use of parathyroid hormone, raloxifene or calcitonin.

[e] n = 117. Due to differences in interview protocols, this question was not asked of all participants.

[f] Frailty category as defined by Fried Frailty Index (Fried et al., 2001) (1 point for each component. Score of 0 = robust; 1–2 = pre-frail; 3+ = frail). Low weight was based on BMI. Exhaustion was based on patient self-report. Low gait speed is based on the 4-meter walking speed test. Low grip strength is measured by hand-held dynamometer. Low physical activity was based on the International Physical Activity Questionnaire (Giles et al., 2008a).

[g] p-Value refers to the difference between the three frailty groups. One-way ANOVA was performed for all variables except for tests of medians where Kruskal-Wallis test was performed.

association between decreased femoral neck BMD and increasing levels of frailty is shown in this table. Lastly, the rates and doses of prednisone use increased with increasing frailty status.

4. Discussion

This study investigated the associations of frailty, BMI, clinical parameters, and laboratory characteristics with femoral neck BMD in a cohort of participants with RA. We found a strong independent association between frailty and decreased femoral neck BMD. Additionally, we found that males had a strong negative independent association between frailty and femoral neck BMD, a finding that was not seen in females. Lastly, among all the individual frailty components, weakness had the strongest association with lower femoral neck BMD.

Measuring frailty provides valuable information into the overall health status of a patient. In the general population, frailty has been shown to be a predictor of poor clinical outcomes including falls, disability and mortality (Strandberg and Pitkälä, 2007). In this study, we found that even when controlling for traditional risk factors for low BMD in RA patients such as age, sex, anti-CCP status, and BMI, that frailty had the strongest association with BMD. Our findings add to those of Li et al. (2019), highlighting the importance of measuring frailty when evaluating osteoporosis and fractures in RA patients. The frailty measure used in our study, the Fried index (Fried et al., 2001), is well-validated and has been used in a wide range of settings and patient populations. Hand grip strength may be influenced by RA disease activity and damage of the hand and no studies have validated hand grip strength as an optimal measure of frailty in this population. We hope to address this issue with future studies aimed at identifying the best method to measure frailty in RA. There were interesting differences between the frailty groups in this study: the pre-frail and frail groups had elevated inflammatory markers, disease activity and levels of obesity compared to the robust group. Additionally, patients in the frail group were taking significantly higher doses of prednisone than the non-frail participants, which could exacerbate frailty and low BMD status. Importantly, because the Fried Index is based on domains that are in themselves risk factors for low BMD and fractures (e.g., muscle strength and physical activity levels), the component assessments offer targets for intervention to prevent both frailty and fractures. Given that body composition measures of ALMI are not routinely available, we believe that measuring frailty may provide valuable insight into a patient's overall health status and risks for poor health outcomes.

Similar to our prior study, we found that factors associated with femoral neck BMD differed between sexes (Wysham et al., 2018). Most notably, in this study, frailty was the most important factor associated with low BMD in males. Furthermore, weakness, as measured by hand grip strength, was the most important frailty category associated with femoral neck BMD, and this relationship was greater in men than women. It is unclear what drives these sex-differences, but we speculate that RA disease severity or reduced sex steroid levels in these

chronically ill males may play a role. Males in this cohort had higher levels of CRP and non-statistically significant increases in prednisone dose and TNF inhibitor use. Although this study is cross-sectional, these findings could suggest that the males in this cohort had more severe RA disease, which may contribute to both the development of frailty and decreased femoral neck BMD. Increased inflammation, pain and glucocorticoid use may also contribute to central hypogonadism, which may play a role our male sub-cohort. This hypothesis is supported by the high rates of altered body composition found in the males in this cohort, previously reported by Baker et al. (Baker et al., 2015; Corona et al., 2016; Isidori et al., 2005). This study was not designed to address these specific questions, but they should be formally tested in future RA cohorts.

Our study was cross-sectional, which allowed us to comment only on associations between study variables and BMD and not causation. Additionally, the self-reported and cross-sectional nature of this study did not allow us to control for disease severity nor cumulative effects of disease activity and inflammation, all of which are likely important factors for the development of both lower BMD and frailty in RA. We were also unable to account for lifetime glucocorticoid exposure, an important risk factor for altered BMD and body composition. We did not include osteoporosis medication use in our primary multivariable model due to the noted inverse association with BMD, which highlights the presence of confounding by indication, but did perform a sensitivity analysis including only participants who did not report taking osteoporosis medications. The results were not substantively different. The smaller sample size of men in this cohort limited analyses that could be conducted on men alone. However, our findings suggest that further attention is needed to the issues of BMD and frailty in men with RA. The population used in this study had longstanding RA with a mean age of onset of 39 years old, as such, it may represent a group with more severe disease, thereby limiting the generalizability of these findings. Finally, our dataset did not include information such as fractures, clinical measurements of disease activity and historical use of medications, data that would useful in further studies of BMD and frailty.

In spite of these limitations, the study had several strengths. This study adds to our previous findings of that high positive anti-CCP is associated with lower femoral neck BMD (Wysham et al., 2018). When adding frailty to the multivariable model, high positive anti-CCP along with more well-established risk factors for low BMD (age, sex and BMI) remain significant. We used both BMI and body composition measures in our models, both of which had similar results, supporting the fact that the clinically-available measure, BMI, may be sufficient for BMD prediction in persons with RA. In our sensitivity analyses both muscle mass (measured by ALMI) and function (measured by hand grip strength) were found to be important factors associated with lower femoral neck BMD. These findings support the idea that both muscle quantity and function are important for bone density (Shin et al., 2011). Overall, our analyses suggest that there are disease-specific factors as well as functional measures, such as those measured by the Fried Index (Fried et al., 2001), that may aid in predicting low BMD and potentially fracture risk in persons with RA.

As the population ages, frailty will impact more patients and managing both frailty and its sequalae will present an increasing challenge to the healthcare system. A better understanding of the prevalence of frailty and its impact on patients with rheumatic conditions will inform treatment decisions given its association with poor health outcomes. Screening patients for frailty may increase the provider's awareness of the patient's functionality and influence the provision of important referrals for gait/fall assessment, as well as evidence-based exercise interventions to improve the frailty phenotype with the ultimate goal of preventing falls and fractures.

5. Conclusions

To our knowledge, this is the first study to describe a strong association between frailty and its subcomponents with BMD in RA. Further studies regarding the impact of frailty on the development of osteoporosis in RA are imperative to provide evidence-based interventions to prevent the outcome of fracture and fracture-associated morbidity and mortality in this high-risk population.

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Disclaimer

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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