Arthritis Increases the Risk for Fractures — Results from the Women's Health Initiative

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ABSTRACT. ***Objective.*** To examine the relationship between arthritis and fracture.

Methods. Women were classified into 3 self-reported groups at baseline: no arthritis (n = 83,295), osteoarthritis (OA; n = 63,402), and rheumatoid arthritis (RA; n = 960). Incident fractures were self-reported throughout followup. Age-adjusted fracture rates by arthritis category were generated, and the Cox proportional hazards model was used to test the association between arthritis and fracture.

Results. After an average of 7.80 years, 24,137 total fractures were reported including 2559 self-reported clinical spinal fractures and 1698 adjudicated hip fractures. For each fracture type, age-adjusted fracture rates were highest in the RA group and lowest in the nonarthritic group. After adjustment for several covariates, report of arthritis was associated with increased risk for spine, hip, and any clinical fractures. Compared to the nonarthritis group, the risk of sustaining any clinical fracture in the OA group was HR 1.09 (95% CI 1.05, 1.13; $p < 0.001$) and HR 1.49 (95% CI 1.26, 1.75; $p < 0.001$) in the RA group. The risk of sustaining a hip fracture was not statistically increased in the OA group (HR 1.11; 95% CI 0.98, 1.25; $p = 0.122$) compared to the nonarthritis group; however, the risk of hip fracture increased significantly (HR 3.03; 95% CI 2.03, 4.51; $p < 0.001$) in the RA group compared to the nonarthritis group.

Conclusion. The increase in fracture risk confirms the importance of fracture prevention in patients with RA and OA. (J Rheumatol First Release May 15 2011; doi:10.3899/jrheum.101196)

Key Indexing Terms:
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With an increasing number of older adults in our society, osteoporosis has become a major public health concern. Fragility fractures, the most devastating outcome associated with osteoporosis, have been shown to lead to increased pain and disability, decreased quality of life[1], and higher mortality rates[2]. Age and bone mineral density (BMD) are the primary risk factors associated with osteoporosis and fragility fractures[3], but others noted in the World Health Organization fracture assessment calculator include sex, weight, height, history of fractures, history of parental hip fracture, smoking, alcohol use, history of secondary osteoporosis, glucocorticoid (GC) use, and the presence of certain comorbid conditions such as rheumatoid arthritis (RA)[1].

RA is a multisystem inflammatory disorder characterized by inflammation and destruction of synovial joints[4]. Patients with RA have lower BMD[5,6,7] and an increased fracture risk compared to nonarthritic controls[8,9,10]. RA affects about 1% of the general population[11], while osteoarthritis (OA), a commonly used arthritic comparison population in RA studies, affects about 30% of adults, making it the most common arthritic condition.

OA is typically not associated with fractures, and was previously considered a "protective" factor against them. Studies by Cumming and Klineberg[12], Dequeker and Johnell[13], and Kanis, *et al*[14] showed a reduction in fracture risk in OA cases, and studies by Jones, *et al*[15] and Arden, *et al*[16] showed no increased or reduced risk in fractures among OA cases. In contrast, Bergink, *et al*[17] and a subsequent study by Arden, *et al*[18] found an increased risk in their OA cases.

Arthritis, in general, is one of the largest public health concerns for aging populations. In the United States, direct and indirect costs attributable to arthritis and other rheumatic con-

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ditions have been estimated to total $128 billion[19], and the number of individuals diagnosed is expected to increase an average of 16% by 2030[20]. If arthritis, particularly OA, is associated with an increased risk of fractures, then the increasing arthritis prevalence would indicate a potential increase in fracture outcomes and associated complications.

Our primary goal was to investigate fracture risk in a group of multiethnic postmenopausal self-reported arthritis cases compared to nonarthritic controls. We tested whether the association is modified by ethnicity or GC use.

MATERIALS AND METHODS

The association between arthritis and fracture was evaluated prospectively using data from the Women's Health Initiative (WHI). The exposure (arthritis status) was self-reported by participants at baseline. The outcome (incident fractures) was reported over the followup period. All participants gave written consent to participate in the WHI, and the University of Arizona Institutional Review Board approved our study.

Women's Health Initiative. The WHI is a nationwide study that investigated the risk factors and preventive strategies of the major contributors to morbidity and mortality in postmenopausal women from the United States, including heart disease, breast and colorectal cancer, and osteoporotic fractures[21]. The WHI recruited 161,808 postmenopausal women aged 50 to 79 years from 40 centers across the country to participate in the clinical trials (CT) component, including the hormone therapy trials, the dietary modification trial, and the calcium and vitamin D trial, or the observational study (OS). Details of recruitment strategies and baseline participant information have been published[22].

Defining arthritis status. The WHI health assessment form was used to identify arthritis status at baseline. The participants were asked, "Did your doctor ever tell you that you have arthritis?", with responses of yes or no. Women responding "yes" were then asked, "What type of arthritis do you have?", with responses of "rheumatoid arthritis" and "other/do not know." For this study, the arthritis exposure variable consists of 3 categories: (1) a nonarthritic control group, including the women who answered "no" to the initial arthritis question; (2) an OA group, including those women answering "yes" to the initial arthritis question and answering "other/do not know" on the arthritis type question; and (3) an RA group, those women reporting RA as arthritis type plus one of the commonly used rheumatologic treatment medications.

Wright and colleagues previously published that the "other/do not know" group serves as the proxy for OA[23], and Walitt and colleagues found that the combination of self-report and medication had the highest positive predictive value (62.2%) for defining RA within the WHI compared to self-report alone[24]. Women were excluded if they did not respond to the initial or followup arthritis question, if they reported RA but did not report one of the treatment medications of interest, or if they reported other rheumatologic or inflammatory arthritic conditions including systemic lupus erythematosus or ulcerative colitis.

Fracture determination. The participants self-reported clinical fractures during periodic medical updates (every 6 months for women participating in the CT, and yearly for the women participating in the OS). The WHI collected information on fractures of the upper and lower arm, elbow, spine, tailbone, hip, upper and lower leg, and foot, but excluded fractures of the ribs, sternum, skull, or face. Centrally trained and masked physicians assessed all fractures reported in the CT and all hip fractures (CT and OS) by review of radiological reports or medical records[25]. The fractures of interest in this analysis included total (all types of fracture), clinical spine, and hip.

Covariates. Variables associated with arthritis and/or fractures were considered as possible covariates including age, race/ethnicity, body mass index (BMI), education, income, physical activity, hospitalizations, number of falls in the previous year, smoking status, alcohol use, hormone use, parental fracture at age > 40 years, total calcium and vitamin D intake, depression score, years since menopause, personal fracture after age 55 years, joint replacements, general health score, and use of certain medications (phenobarbital, anticonvulsants, anti-Parkinson drugs, antidepressants, antianxiety drugs, thyroid medications, thiazolidinediones, proton pump inhibitors, thiazide diuretics, statins, bisphosphonates, calcitonins, nonsteroidal antiinflammatory drugs, estrogens, heparin, and selective-estrogen receptor modulators).

All covariates were assessed at baseline. Height and weight were measured using standardized procedures by WHI clinical staff, and were used to calculate BMI (kg/m^2). Race/ethnicity was classified into 6 categories: American Indian or Alaskan Native, Asian or Pacific Islander, African American, Hispanic/Latino, White (not of Hispanic origin), or other. Women reported highest level of education completed, if they had been hospitalized in the last 2 years (yes or no), fracture at age of 55 years or older (yes or no), and the number of times they fell to the ground in the past 12 months (0, 1, 2, ≥ 3). Summary variables were generated based on questions regarding parental fractures (yes or no), physical activity (metabolic equivalence units per week), hormone use (never, past, or current user), smoking status (non, past, or current smoker), and alcohol use (non, past, or current drinker). Years since menopause was calculated based on reported last menstrual period. Questions from the Rand 36-Item Health Survey were used to compute a general health measure, and questions from the Center for Epidemiologic Studies Depression Scale (CES-D) were used to calculate a depression score. Dietary calcium and vitamin D amounts generated from food frequency questionnaire data were combined with amounts reported from supplemental use to generate total calcium and vitamin D variables. Binary variables for each class of drugs were used. Bisphosphonates and calcitonin were combined to create an osteoporosis medication summary variable. Variables related to the WHI design, such as clinical trial assignment (not randomized, placebo, or intervention), were also included as covariates.

Statistical analysis. Descriptive statistics by arthritis group were performed using ANOVA for continuous variables and chi-squared tests for categorical variables. Age-adjusted fracture rates and 95% CI by arthritis group were calculated using direct standardization. Cox proportional hazards models were used to test difference in risk of fracture among groups. Days from randomization to fracture served as the event time, and days from randomization to last contact served as the censoring time for those who did not fracture. Marginal analyses were performed for each covariate, which was included in the full model if the covariate was significant ($p < 0.2$ at the 0.05-α level) in a 2-sided test. Backward elimination techniques were used to produce the final model, including all variables statistically ($p < 0.05$) or biologically significant. Survival estimates were generated to graphically portray group differences in fracture risk. Ethnicity and GC interactions were tested using cross-product interaction terms (e.g., arthritis*ethnicity) and stratified analyses. All analyses were performed in Stata v. 10 (StataCorp, College Station, TX, USA).

RESULTS

Of the 161,808 women enrolled in the WHI, 147,657 were not missing arthritis information and did not report systemic lupus erythematosus or ulcerative colitis. Of them, 83,295 (56.4%) were included in the nonarthritic control group. Of the women who reported arthritis, 63,402 (43.0%) were placed in the OA group, and 960 women (0.65%) met the criteria for the RA group. All other women were excluded from analyses.

Differences in baseline demographic and lifestyle variables were present by arthritis group. The OA and RA groups were significantly older than the nonarthritic control group, with the OA group being on average 2.92 years older (Bonferroni p value < 0.001) than the nonarthritic control group, and the RA group being on average 2.86 years older (Bonferroni p value < 0.001) than the nonarthritic controls. The arthritis

groups had a larger percentage of African Americans compared to the nonarthritic control group (RA: 13.2%, OA: 9.3%, nonarthritic control: 8.2%). In a posthoc chi-squared test, the percentage of African Americans in the OA group was found to be significantly higher than in the nonarthritis group ($p < 0.001$), and similarly the percentage of African Americans in the RA group was significantly higher ($p < 0.001$) than in the nonarthritis group. The OA group had the highest mean weight (75.5 kg), followed by the RA group (73.2 kg) and the nonarthritic control group (71.7 kg). The weight of the OA group was significantly higher than that of the nonarthritis group (Bonferroni p value < 0.001) and the RA group (Bonferroni p value < 0.001), and the RA weight was significantly higher than that of the nonarthritis group (Bonferroni p value = 0.025). There were statistically significant differences in the percentage of hospitalization in the last 2 years (RA: 28.0%, OA: 18.4%, no arthritis: 11.6%; overall $p < 0.001$) and history of fracture at ≥ 55 years of age (RA: 20.0%, OA 18.8%, no arthritis 14.1%; overall $p < 0.001$). Complete descriptive information with overall ANOVA and chi-squared test p values can be found in Tables 1 and 2.

Fractures in the WHI. As of March 2008, the women were followed for a mean of 7.80 (SD 1.54) years. There were 24,137 clinical fractures of any type, among them 2559 of the spine and 1698 of the hip (Table 3). The age-adjusted rate per 100 person-years for sustaining total fractures (fracture of any type) was 2.11 (95% CI 2.08, 2.15) in the nonarthritic control group, increasing to 2.51 (95% CI 2.46, 2.55) in the OA group, and 3.64 (95% CI 3.17, 4.11) in the RA group (Figure 1A). The age-adjusted spine fracture rate increased from 0.19 to 0.26 per 100 person-years between the control group and the OA group, and increased again to 0.50 per 100 person-years in the RA group (Figure 1B). There was no difference in hip fracture rates between the control group and the OA group (0.14/100 vs 0.16/100, respectively), but there was an increase in the hip fracture rate in the RA group (0.51/100; Figure 1C).

Testing the association between arthritis and fracture risk. No significant interaction between ethnicity or GC use was found in the association between arthritis and fracture. Covariates included in the final Cox proportional hazards model included age, race/ethnicity, BMI, physical activity, assignment in all clinical trials, hospitalizations, number of falls, smoking status, hormone use, parental fracture > age 40, personal fracture ≥ age 55, total calcium and vitamin D intake, depression score, years since menopause, joint replacements, use of diabetic and osteoporosis medications, and general health score. In comparison to the nonarthritic control group, there was a significant risk for sustaining any type of fracture in both the OA (HR 1.09; 95% CI 1.05, 1.13) and RA groups (HR 1.49; 95% CI 1.26, 1.75; Table 4). In comparison to the nonarthritic control group, the risk of clinical spine fracture was 1.17 (95% CI 1.05, 1.29, $p = 0.004$) and 1.93 (95% CI 1.29, 2.90, $p = 0.001$) in OA and RA groups, respectively (Table 4). No significant increase in hip fracture risk was observed in the OA group (HR 1.11; 95% CI 0.98, 1.25) compared to the nonarthritic control group; however, a highly significant increase in hip fracture risk (HR 3.03; 95% CI 2.03, 4.51) was observed in the RA group compared to the nonarthritic control group (Table 4).

DISCUSSION

In this large population of postmenopausal women, self-reported arthritis is associated with significant increase in fracture risk in women reporting OA and RA. After controlling for several covariates, the RA group had a highly significant increased risk of all fractures studied (HR total 1.49, HR spine 1.93, HR hip 3.03) in comparison to the nonarthritis group. Modest significant increases in total (HR 1.09) and clinical spine (HR 1.17) fracture risk were seen in the OA group in comparison to the nonarthritis group, but no significant increase in hip fracture risk was seen. The associations found between arthritis and fracture were not modified by race, ethnicity, or GC use in our study.

The RA findings are consistent with the literature, showing an increased risk of fractures in patients with RA[9,10,26]. Incidence of any, spine, and hip fracture in the Consortium of Rheumatology Researchers of North America (CORRONA) registry was reported to be 3.71, 0.78, and 0.66 per 100 person-years, respectively[27]. The age-adjusted fracture rates for the RA group were 3.64, 0.49, and 0.50 per 100 person-years for total, spine, and hip fracture in the WHI, and although the CORRONA registry includes premenopausal women and men, the incidence rates of the nationwide CORRONA registry are comparable to the rates found in the WHI.

General lifestyle and demographic osteoporosis risk factors, such as age, smoking, and physical activity, play a significant role in fracture risk[1], but the primary risk factor for fracture is low BMD. It has been well documented that patients with RA have lower BMD at many skeletal sites compared to various control populations[6,7,28], and although we did not examine BMD, it is highly probable that the associations seen are in part driven by BMD. A sensitivity analysis in the participants from 3 WHI clinical centers with available BMD measurements was proposed; however, it could not be adequately completed because of the low frequency of fractures (total fractures, 22; clinical spine fractures, 2; hip fractures, 3) in the smaller RA group (n = 78).

The risk of sustaining any clinical fracture and a spinal fracture was modestly but significantly increased in the OA group compared to the nonarthritic controls. It is likely that the effects of OA on fracture rate are underestimated in this study because of the misclassification inherent in self-reporting OA. As mentioned, the association between OA and fracture has been mixed in the literature. The most recent study to suggest that OA increases the risk of fractures, by Arden and colleagues, found that after adjustment for falls and the use of walking aids, patients with clinician-diagnosed knee OA had a significant risk for nonvertebral fractures (1.48; 95% CI

Table 1. Baseline characteristics of categorical variables by arthritis status. All variables are significantly different among the 3 groups at $p < 0.001$, with the exception of thiazolidinediones ($p = 0.020$).

Characteristics	No Arthritis, n = 83,295		OA, n = 63,402		RA, n = 960	
	N	%	N	%	N	%
Baseline age group, yrs						
50–59	33,804	40.58	15,378	24.25	240	25.00
60–69	35,446	42.55	30,248	47.71	448	46.67
70-79	14,045	16.86	17,776	28.04	272	28.33
Race/ethnicity						
White	68,699	82.68	53,153	84.05	741	77.35
Hispanic	3573	4.30	2060	3.26	38	3.97
African American	6817	8.20	5857	9.26	126	13.15
Asian	2721	3.28	1191	1.88	26	2.71
American Indian	317	0.38	292	0.46	9	0.94
Unknown	967	1.16	686	1.09	18	1.88
Hormone trial						
Not randomized	68,819	82.62	53,487	84.36	878	91.46
Intervention	7374	8.85	4887	7.71	41	4.27
Control	7102	8.53	5028	7.93	41	4.27
Dietary modification trial						
Not randomized	57,310	68.80	45,779	72.20	812	84.58
Intervention	10398	12.48	7069	11.15	59	6.15
Control	15587	18.71	10554	16.65	89	9.27
Calcium and vitamin D trial						
Not randomized	63,522	76.26	50,503	79.66	866	90.21
Intervention	9906	11.89	6434	10.15	53	5.52
Control	9867	11.85	6465	10.20	41	4.27
Hospitalized in last 2 years						
No	69,909	88.43	51,453	81.59	683	72.05
Yes	9143	11.57	11,607	18.41	265	27.95
No. falls in 12 months						
0	57,007	71.34	40,530	64.10	612	64.15
1	15,054	18.84	13,331	21.08	201	21.07
2	5454	6.83	6123	9.68	97	10.17
3+	2398	3.00	3248	5.14	44	4.61
Parental fracture at age 40+						
No	47,303	61.00	34,447	59.34	547	62.37
Yes	30,242	39.00	23,605	40.66	330	37.63
Fracture at age 55+ yrs						
No	52,476	85.93	43,140	81.24	631	80.08
Yes	8595	14.07	9961	18.76	157	19.92
Smoking status						
Never smoked	42,597	51.69	31,502	50.34	437	46.00
Past smoker	33,770	40.98	27,124	43.35	443	46.63
Current smoker	6046	7.34	3947	6.31	70	7.37
Hormone therapy use						
Never used	37,413	44.95	26,774	42.27	397	41.40
Past user	12,221	14.68	10,979	17.33	161	16.79
Current user	33,593	40.36	25,589	40.40	401	41.81
Osteoporosis medications use						
No	81,787	98.19	61,653	97.24	892	92.92
Yes	1508	1.81	1749	2.76	68	7.08
Thiazolidinediones use						
No	83,240	99.93	63,339	99.90	958	99.79
Yes	55	0.07	63	0.10	2	0.21
Previous joint replacement						
No	77,918	99.20	58,604	93.29	773	81.28
Yes	628	0.80	4218	6.71	178	18.72

OA: osteoarthritis; RA: rheumatoid arthritis.

Table 2. Baseline characteristics of continuous variables by arthritis status. All variables significantly different among the 3 groups at $p < 0.001$.

Characteristic	No Arthritis, n = 83,295		OA, n = 63,402		RA, n = 960	
	Mean	SD	Mean	SD	Mean	SD
Age, yrs	61.89	7.14	64.81	7.01	64.75	7.12
Height, cm	162.00	6.58	161.50	6.73	161.10	6.76
Weight, kg	71.74	15.94	75.45	17.71	73.18	17.78
Body mass index, kg/m^2	27.19	5.49	28.78	6.28	28.10	6.40
Years since menopause	13.60	9.36	16.90	9.62	16.71	9.97
Total calcium intake, mg	1148.00	750.00	1207	734.10	1264.00	837.60
Total vitamin D intake, mg	8.92	6.87	9.66	7.12	9.88	6.84
CES-D	0.03	0.11	0.05	0.14	0.05	0.14
Total physical activity per wk (METS)	13.35	14.34	11.53	12.92	9.58	11.46
General health score	78.52	16.00	70.03	18.07	57.26	20.35

OA: osteoarthritis; RA: rheumatoid arthritis; CES-D: Center for Epidemiologic Studies Depression Scale; METS: metabolic equivalence units.

Table 3. Frequency of fracture in the subjects assessed under the Women's Health Initiative, sorted by arthritis status.

Location	No Arthritis, n = 83,295		OA, n = 63,402		RA, n = 960			Total Population, n = 147,657	
	N	%	N	%	N	%	p	N	%
Any fracture	12,411	14.9	11,488	18.1	238	24.8	< 0.001	24,137	16.3
Clinical spine	1126	1.4	1395	2.2	38	4.0	< 0.001	2559	1.7
Hip	775	0.9	885	1.4	38	4.0	< 0.001	1698	1.1

OA: osteoarthritis; RA: rheumatoid arthritis.

1.00, 2.19), and no significant association was seen between clinician-diagnosed knee OA and risk for hip fracture (1.84; 95% CI 0.78, 4.34)[18]. Although our results are in agreement with the Arden study, the use of patients with clinically diagnosed, site-specific OA yielded higher fracture estimates than those found in our study using self-reported OA cases.

In contrast, the most recent study showing a protective effect of OA on fracture risk was a case-control population-based study conducted in Denmark. After adjustment for several variables, Vestergaard and colleagues found a significant risk reduction for any fracture and hip and spine fractures in participants with OA duration > 2 years[29]. Population demographics could be the primary explanation for the difference associations seen between the Vestergaard study and our report, as the Danish population used was almost 20 years younger than the WHI population.

Although a consensus has not been reached, several biological mechanisms have been proposed relating OA to fracture. Like RA, the increase in fracture in patients with OA could be driven through a BMD pathway. Studies have shown that BMD in OA populations is typically higher than that in nonarthritic populations[30,31,32]; therefore, this argument does not provide a good explanation for increases in fracture. Although patients with OA have a higher BMD, the quality or strength of the bones may be compromised compared to other arthritic and nonarthritic populations. Javaid and colleagues assessed hip structural geometry as a marker of bone strength in a group of patients with OA and found that alterations in geometry precede OA diagnosis[33], suggesting that a biological process involved in OA potentially alters bone strength.

Falling is another proposed OA fracture mechanism. OA, especially at sites such as the knee and hip, is associated with increased pain, decreased postural stability, and decreased muscle strength, all of which have been shown to be significant contributors to fall risk[34,35,36]. Falling is a well documented risk factor for fractures[1], and early studies have shown that the self-report of OA is associated with increased risk of falls[37,38]. Foley and colleagues did not see increased risk for falls in cases of radiographic knee and hip OA, but did see that report of pain is highly associated with falls and that patients with OA reported more pain[39].

One last possibility is that our results represent the consequences related to behavioral and physiologic changes that occur in individuals who perceive articular discomfort they classify as arthritis. Poor self-rated health has been shown to be an independent risk factor for fractures in many studies[40,41,42,43,44]. It is possible that self-reported arthritis in the WHI is a measure of autoperception that encompasses a variety of health domains, such as pain, balance confidence, self-efficacy, and functional status.

Strengths and limitations. Our study has several limitations related to the arthritis exposure. The limitations associated with self-report of OA and the use of a proxy measure of OA within the WHI described by Wright and colleagues apply to this analysis[23]. Walitt and colleagues also found that self-reported OA in the WHI was very sensitive (95.0%), but

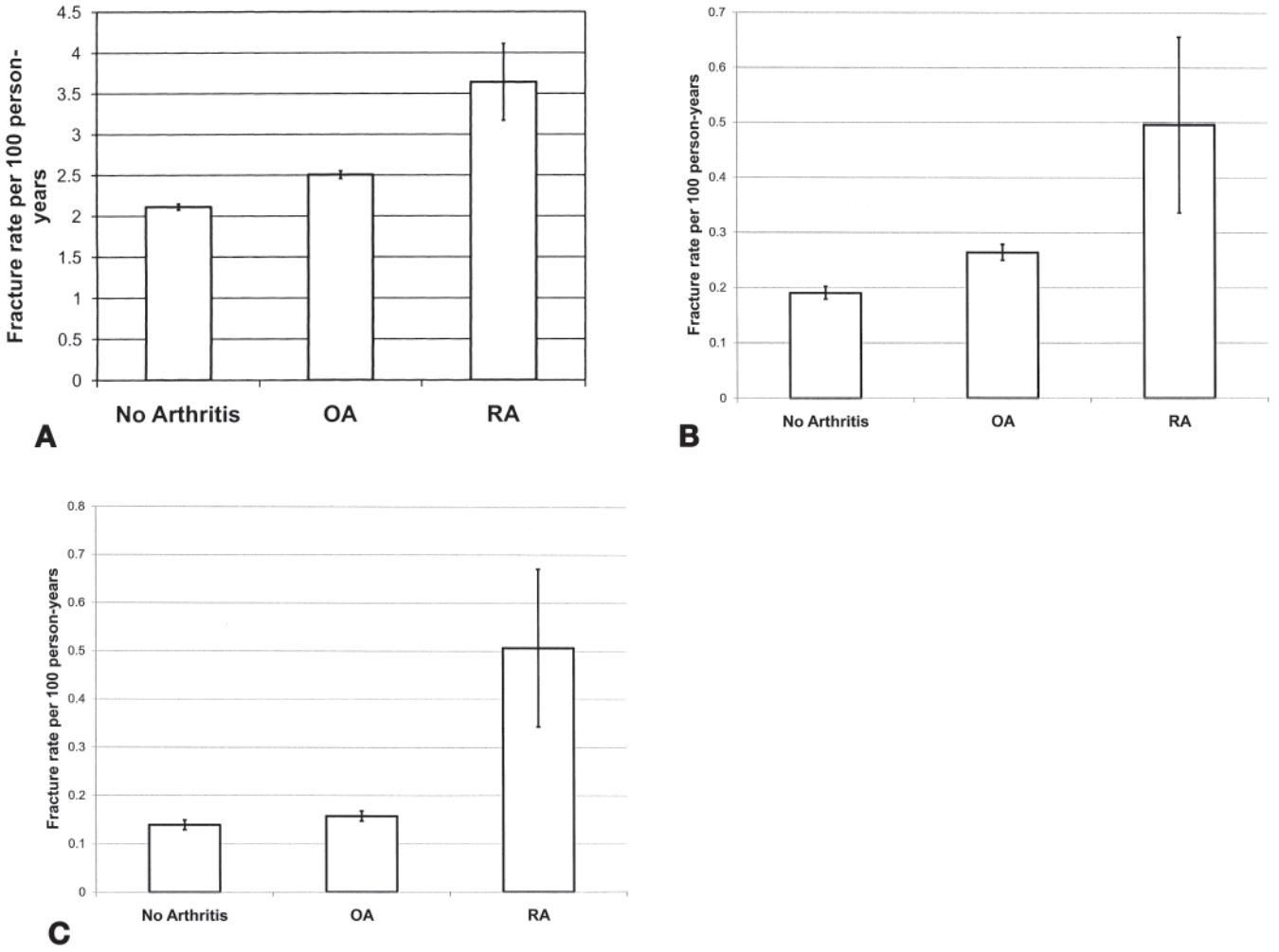

Figure 1. Fracture rates by arthritis status. Age-adjusted rates per 100 person-years and 95% CI. OA: osteoarthritis; RA: rheumatoid arthritis.

not particularly specific (23.4%), and had only fair agreement between self-reported OA and chart review ($\kappa = 0.23$; unpublished data). The potential for the moderate amount of misclassification in the OA group would bias the results of this study to the null. People experiencing joint pain because of a previous injury, or having other soft-tissue conditions such as tendonitis or other noninflammatory arthritic conditions, may report having OA even though it has not been clinically diagnosed. This could also lead to a moderate amount of misclassification, again biasing the estimates toward the null.

Not having site-specific or radiographically confirmed OA cases is another limitation of this study. Fracture risk is probably different for persons with OA of the hip compared to persons with knee, hand, or spine OA. The OA-affected area may

Table 4. The risk of fracture by arthritis group. Data were adjusted for age; race; body mass index; physical activity; assignment in the hormone therapy trials, the dietary modification trial, and the calcium and vitamin D trial; hospitalizations; falls; smoking; hormone use; parental fracture at > age 40 years; calcium and vitamin D intake; depression score; years since menopause; diabetic treatments; osteoporosis medication; general health score; fracture at > age 55 years; and joint replacements.

Location	No Arthritis, n = 83,295	OA, n = 63,402		RA, n = 960	
		HR (95% CI)	p	HR (95% CI)	p
Any fracture, n = 24,137	Reference	1.09 (1.05, 1.13)	< 0.001	1.49 (1.26, 1.75)	< 0.001
Spine, n = 2559	Reference	1.17 (1.05, 1.29)	0.004	1.93 (1.29, 2.90)	0.001
Hip, n = 1698	Reference	1.11 (0.98, 1.25)	0.105	3.03 (2.03, 4.51)	< 0.001

OA: osteoarthritis; RA: rheumatoid arthritis.

have a higher BMD, while regions without OA have normal or low BMD, potentially altering overall fracture risk.

Regarding the RA classification, the use of medication in the RA definition probably revealed true cases of RA, but these may represent the more severe cases, potentially overestimating the effect of RA on fracture risk. We did not take into account incident cases of arthritis and the effect it has on fracture risk, nor the additive or multiplicative effect of having both conditions on fracture risk.

The use of self-reported fracture outcomes can also be seen as a limitation. Sensitivity analyses were performed using adjudicated fractures only. Slight changes in the point estimates were observed with the smaller sample size, but the overall conclusions did not change. Chen and colleagues found high agreement between self-report and adjudicated fractures in a WHI substudy[45], assuring high quality of the fracture data used in our study.

Our study adjusted for several covariates, but was unable to adjust for GC use, as it was used in the definition of the RA group. To test the possible interaction of GC in the relationship between arthritis and fracture, a categorical variable was created separating users and nonusers in each arthritis group (data not shown). Although no interaction was present, the point estimate of the fracture risk was higher in GC users compared to nonusers, and by not adjusting for GC, the true fracture risk for women not taking GC was overestimated and the risk was underestimated for women using GC.

Although limited by these factors, our study has many strengths. The most notable is the size of the WHI and the size of each of the exposure groups. Having > 63,000 women in the OA group gave more than adequate power to estimate the effects OA has on fracture outcomes. Although not clinically determined, the prevalence of OA in the WHI population was about 43%, comparable to the 42% prevalence of radiographic OA in the hands, knees, and hips of the women age 60 years and older participating in the National Health and Nutrition Examination Survey-III[46]. The OA limitations presented would have resulted in estimates being biased toward the null; however, significant association remained in our study. Although not reaching general population prevalence estimates, the RA group sample size was large enough to confirm the association between RA and fracture. The WHI also had a larger percentage of women from minority groups, which allowed examination of effect modification by race and ethnicity. The women of the WHI were followed on average almost 8 years, ensuring adequate numbers of fracture outcomes, especially for the more rare hip fracture outcome.

Arthritis and osteoporosis are important public health concerns for older adults. OA and RA affect > 25 million adults in the United States, and fractures cost billions of healthcare dollars annually. The increase in fracture risk found in our study confirms the importance of fracture prevention in patients with RA and OA.

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APPENDIX

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