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Hip Osteoarthritis and the Risk of All-Cause and Disease-Specific Mortality in Older Women: Population-Based Cohort Study

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Abstract

Objectives—Determine the risk of all-cause and disease-specific mortality among older women with hip OA and identify mediators in the causal pathway.

Methods—Data were from the Study of Osteoporotic Fractures, a US population-based cohort study of 9704 white women, aged 65 years. The analytic sample included women with hip radiographs at baseline (N=7,889) and year 8 (N=5,749). Mortality was confirmed through October 2013 by death certificates and hospital discharge summaries. Radiographic hip OA (RHOA) was defined as having Croft grade 2 in at least 1 hip (definite joint space narrowing or osteophytes plus 1 other radiographic feature).

Results—Mean follow-up time was 16.1 ±6.2 years. Baseline and year 8 prevalence of RHOA was 8.0% and 11.0%, respectively. Cumulative incidence (proportion of deaths during study

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period) was 67.7% for all-cause mortality, 26.3% for cardiovascular disease (CVD) mortality, 11.7% for cancer mortality, 1.9% for gastrointestinal disease mortality, and 27.8% for all other mortality causes. RHOA was associated with an increased risk of all-cause (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.05–1.24), and CVD (HR, 1.24; 95% CI, 1.09–1.41) mortality adjusted for age, body mass index, education, smoking, health status, diabetes, and stroke. These associations were partially explained by physical function (mediating variable).

Conclusion—RHOA was associated with an increased risk of all-cause and CVD mortality among older white women followed for 16 years. Dissemination of evidence-based physical activity and self-management interventions for hip OA in community and clinical settings can improve physical function and might also contribute to lower mortality.

Keywords

Cardiovascular Disease; Epidemiology; Mortality; Osteoarthritis; Physical Function

Osteoarthritis (OA) affects approximately 27 million adults in the United States⁽¹⁾ and is characterized by osteophyte formation and cartilage degradation that primarily affects the knees, hips, and small joints of the hand, resulting in joint pain, swelling, and stiffness. People with OA are also more likely to have certain comorbid conditions (eg, obesity, heart disease, and gastrointestinal diseases) than those without OA.⁽²⁾

The morbidity-related burden of OA is well documented and includes poor function, impairments in activities of daily living and other physical disabilities; however few population-based longitudinal studies have tested whether radiographically measured OA is associated with an increased risk of mortality.^(3, 4) A systematic review⁽⁵⁾ of 9 studies concluded that there was moderate evidence of an association between OA and mortality, particularly mortality due to acute cardiovascular and gastrointestinal causes, but noted methodological shortcomings across these studies, including lack of accounting for potential confounders, samples that were not population-based, short follow-up times, and insufficient statistical power.

The annual prevalence of radiographic hip OA (RHOA) in several cohort studies (of primarily older adults) has been reported to range from 8% to 28%.^(6–8) Hip OA is the most common reason for total hip replacement, and the annual costs from hip replacements are predicted to reach \$21 billion by 2015 in the United States alone.⁽⁹⁾

We tested the hypothesis that older white women with RHOA were at an increased risk of all-cause mortality as well as disease-specific mortality (from cardiovascular disease [CVD], cancer, gastrointestinal [GI] disease, and other causes). In addition, we examined the potential mediating role of five characteristics (physical activity, physical function, disability, hip pain, and non-steroidal anti-inflammatory drug (NSAID) use) in the causal pathway between OA and mortality.

MATERIALS and METHODS

Study population

The Study of Osteoporotic Fractures (SOF) is a prospective population-based cohort study of women aged 65 years or older who were recruited from 4 metropolitan areas in the United States: Baltimore, MD; Pittsburgh, PA; Minneapolis, MN; and Portland, OR. All data were collected at the 4 clinical centers using a common protocol and detailed manuals of operation.(10) The original cohort comprised 9704 white women recruited in 1986–1988 who had not undergone bilateral hip replacement and were able to walk without assistance. Hip radiographs were obtained at both baseline (1986–1988) (n=7889) and year 8 (visit 5) (1995–1996) (n=5749) (Figure 1). The protocol and consent form were approved by the Institutional Review Boards at all participating institutions.(10) All participants provided written informed consent. (11)

Mortality

Following baseline, participants were contacted by mail or telephone every 4 months to ascertain outcome information (including mortality) and address changes. For all deaths, we obtained a death certificate and hospital discharge summary (if available) and submitted them to the coordinating center at the University of California San Francisco for central adjudication. Deaths were ascertained through October 2013, and follow-up rates were greater than 95% for vital status. The underlying causes of death were coded using the International Classification of Diseases 9th Revision (ICD) and all-cause mortality was ascertained along with 4 subcategories of death: 3 disease-specific causes (CVD, ICD-9 390–459.9, cancer, ICD-9 140–239.9, GI disease, ICD-9 520–579) and all other causes. CVD mortality included both heart disease and cerebrovascular disease.

Hip Osteoarthritis

Participants had a supine anteroposterior radiograph of the pelvis with the hips in 15–30° of internal rotation. On both the baseline and follow-up radiographs, each hip was rated for joint space narrowing (JSN) in 2 locations (superolateral and superomedial joint space) and osteophytes in four locations (lateral femoral, lateral acetabular, inferior femoral, and inferior acetabular) and graded using both Croft and Kellgren-Lawrence (K/L) grades. Radiograph pairs were read side-by-side by 1 primary reader (NEL) who was blinded to the order and identifying information of the films. All radiograph pairs with either definite osteophytes or definite JSN (score ≥ 2) in any location on either film were reevaluated by 2 readers (NEL, MCH) to reach a consensus score. To improve the validity of the readings, twenty-one percent of film pairs were selected for consensus reading.(12) A summary Croft grade of 0–4 was assigned to each hip based on 5 radiographic features: 1) JSN; 2) osteophytes; 3) subchondral sclerosis; 4) cysts formation; and 5) deformity.(13) RHOA was defined as a Croft grade ≥ 2 in at least 1 hip, at either baseline or year 8, which required the presence of either definite JSN or definite osteophytes plus at least 1 other radiographic feature.(14) A Croft grade ≥ 2 for defining RHOA has shown high construct and predictive validity in prior analyses,(15) and sufficient statistical power for the current analysis. Interrater reliability for the summary Croft grade ≥ 2 using the kappa (κ) statistic, on a random sample of 178 film pairs, was very good ($\kappa=0.65$). (14) A summary K/L grade of 0–

4 was assigned, with a score of 2 indicating RHOA (definite JSN and osteophytes).(16) For those having a total hip replacement (THR) between baseline and year 8 a reason for the procedure was determined, thus, women with RHOA at baseline and subsequent THR because of RHOA (n=36) were classified as having RHOA at year 8 despite no radiograph on that particular hip. The cause of THR after year 8 was not given, and therefore, women with no RHOA at year 8 and THR after this visit (n=111) were censored at time of THR.

Potential Confounders

Eleven potential confounders related to both hip OA and mortality, but not likely in the causal pathway(3–5), were selected *a priori* for consideration in multivariate models. All variables were measured at baseline and year 8, with the exception of education (<college/college) (unlikely to change over time). Age, current smoking (yes/no), health status (excellent/good vs. fair/poor/very poor), history (yes/no) of diabetes, stroke, chronic obstructive pulmonary disease (COPD), osteoporosis, estrogen use, and calcium use, were ascertained through self-report. Body mass index (BMI) was calculated using measured weight (balance beam scale) and height (Harpenden stadiometer), and obesity was defined as having a BMI ≥ 30 kg/m². Fracture history since age 50 years was measured by self-report at baseline and adjudicated incident fractures from baseline to year 8.

Potential Mediators

We considered 5 characteristics (measured at baseline and year 8) as potential mediators in the causal pathway between RHOA and mortality: 1) physical activity (measured in in block kcal/week burned from walking), 2) objectively measured physical function (assessed as the speed (meters/second) to complete a 6 meter walk 3) disability 4) hip pain (self-reported hip pain on most days for at least one month in the past year), and 5) NSAID use. Disability was measured using five instrumental activities of daily living (IADLs): walking two to three blocks on level ground, climbing up 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing. Yes responses to not being able to perform activities were summed for a score range of 0–5 for IADLs and treated as a continuous variable.(17)

Statistical Analysis

Characteristics of women with and without hip RHOA at baseline were compared using χ^2 tests, 2-sample *t* tests, or Wilcoxon rank sum tests (for data with non-normal distributions). To assess potential selection bias, characteristics of women with and without radiographs at baseline were compared. Mortality in those with RHOA compared with those without RHOA was estimated using hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards regression with time-varying covariates (baseline and year 8), which takes both values into account. Each disease-specific mortality model accounted for the other 3 competing causes of mortality by using the Lunn and McNeil stratified augmented data approach.(18) Treating competing causes of death as non-informative censoring (not accounting for why a respondent left the cohort and furthermore assuming that it is not associated with the outcome of interest) is inappropriate. That is, once a respondent dies from a competing cause of death, cumulative incidence of mortality due to the condition of interest will be overestimated.(19) The proportional hazards assumption

was confirmed graphically and formally using Schoenfeld residuals. The model fit was verified by plotting the Nelson-Aalen cumulative hazard of the Cox-Snell residuals.

We tested for potential interactions between age (65–74 vs. ≥75 y) and RHOA status, and BMI (obese vs. non-obese) and RHOA status, but these were not significant and thus, analyses were not stratified by age or BMI. The multivariate (MV) regression model included potential confounders associated with RHOA at α .05 (eg, age, health status, and diabetes) or potential confounders that have been shown to be associated with mortality (eg, BMI, smoking, education, and stroke).^(20, 21) Time-varying covariates not ascertained at baseline and year 8 could not be considered for inclusion in MV models. To investigate mechanisms by which RHOA might be associated with mortality; we used marginal structural models to estimate the amount of mediation⁽²²⁾ (i.e., the indirect effect) for each potential mediator individually, while controlling for selected potential confounders in the MV models. For context, the direct effect would be the effect of RHOA on mortality outcomes not taking into account mediation, and the total effect would be the summation of the direct and indirect effects. For each potential mediating variable we estimated the percent of the association between RHOA and mortality that can be explained by the mediator using the following formula: $(HR_{\text{indirect effect}}/HR_{\text{total effect}})*100$. Mediation analyses were limited to mortality outcomes that were statistically significant in the MV analyses.

Two sensitivity analyses were performed. One excluded all women who reported a THR during the study to determine if the effect of RHOA on mortality is greater when the potential protective impact of THR on mortality is not factored into the analysis.^(23, 24) The second compared findings of the Croft vs. K/L scales for assigning RHOA to see if they differed. Statistical significance for all analyses was set at α .05.

RESULTS

From the original, full SOF cohort, women without (compared with women with) radiographs at baseline were significantly older, had lower education, had poorer health, were more likely to have at least one of 5 comorbidities, were less likely to use calcium or estrogen, were less physically active, had poorer physical function, had greater disability, and were more likely to die during the study (Table 1).

The 7,889 women with hip radiographs at baseline had a mean follow-up time of 16.1 ± 6.2 years. The prevalence of RHOA was 8.0% at baseline and 11.0% at year 8. Women with RHOA at baseline (compared with those without RHOA at baseline) were significantly older and had poorer health, higher prevalence of diabetes, were less physically active, had poorer physical function, had greater disability, were more likely to report hip pain, and a higher cumulative incidence of death (74.5% vs. 67.2%) (Table 1).

Mortality

RHOA was associated with increased risk of all-cause (HR, 1.14; 95% CI, 1.05–1.24) and CVD (HR, 1.24; 95% CI, 1.09–1.41) mortality after adjusting for age, body mass index, education, smoking status, health status, diabetes, and stroke (Table 2). RHOA was not

associated with mortality risk due to cancer (HR, 1.18; 95% CI, 0.96–1.45) or to GI disease (HR, 1.25; 95% CI, 0.77–2.03) (Table 2).

The indirect effect of RHOA on all-cause and CVD mortality (via its effect on physical function) was HR, 1.06; 95% CI, 1.02–1.10 and HR, 1.06; 95% CI, 1.00–1.13, respectively (Table 3). As a result, 42.9% and 25.0% of the increased risk of all-cause and CVD mortality (among women with RHOA) could be explained by poor physical function. There was no evidence that the associations between RHOA and mortality were mediated by physical activity, disability, hip pain, or NSAID use.

Sensitivity analyses

The first sensitivity analysis (excluding women with THR and using the RHOA definition of Croft 2) showed that RHOA was associated with all-cause and CVD mortality.

Additionally, increased risk of cancer mortality was significant (Table 2). In MV models, RHOA was associated with increased risk of all-cause (HR, 1.24; 95% CI, 1.13–1.35), CVD (HR, 1.30; 95% CI, 1.14–1.50), and cancer mortality (HR, 1.30; 95% CI, 1.05–1.61). RHOA was not associated with GI disease mortality (HR, 1.36; 95% CI, 0.82–2.27) or all other cause mortality (HR, 1.14; 95% CI, 0.98–1.31).

RHOA (defined as K/L 2 rather than our original Croft 2) was significantly associated with CVD mortality (HR, 1.24; 95% CI, 1.05–1.45) but not all-cause, cancer, GI disease, or all other cause mortality (Table 2).

DISCUSSION

In this population-based prospective cohort study (average follow-up of 16 years), RHOA was associated with an increased risk of all-cause and CVD mortality among older white women after controlling for several potential confounders. There was evidence that the impact of RHOA on mortality was in part due to its effect on physical function.

Determining if OA increases risk of all-cause or disease-specific mortality has major public health and clinical implications. Only about 1 in 10 adults with OA meet physical activity recommendations (150 min/week moderate-equivalent activity) using accelerometer data(25), and participating in recommended levels of physical activity is associated with improved physical function and reduced risk of mortality.(26) Physical activity interventions have been developed specifically to help people with arthritis increase their physical activity and improve physical function and reduce pain.(27) Additionally, participation in self-management education programs has been shown to lead to increased levels of physical activity and improved self-rated health, which have both been linked to reduced mortality risk.(28, 29)

Other relevant literature is relatively sparse. A study using a population-based cohort design among 1163 participants ages 35 years and older in southwest England, reported excess all-cause mortality among adults with OA compared with the general population.(4) Comparing findings from our study and that one is difficult because of several methodological differences: 1) the English study did not evaluate the longitudinal association between OA

(OA vs. non-OA) and mortality, 2) the study population they used was limited to participants who reported hip or knee pain at baseline, which has major implications for internal validity and generalizability, 3) the age of their cohort was much younger than our study population, and 4) they measured OA status at baseline only, which is subject to change over a 15-year follow-up. More recently, a cohort from the Framingham study did not find an association between hand OA and all-cause mortality using a sample of 1,348 men and women, mean age 62.2 years, and median follow-up 16.0 years.(3)

This is the first study to our knowledge to examine directly and prospectively the effect of OA on disease-specific mortality in the same population-based cohort, as opposed to studies that examine the relationships indirectly comparing disease-specific mortality rates from a standard population, an approach that is subject to substantial bias.(30) In our study, women with RHOA had a 24% increased risk of CVD mortality in multivariate models. This finding is consistent with a report on excess cardiovascular mortality(4) and 2 studies on OA and incident CVD,(3, 31) but contrary to the Rotterdam study which showed that disability, not OA, predicts CVD.(32) Poor physical function among adults with OA may explain this increased risk of CVD mortality.(33)

For years OA was recognized as a form of degenerative arthritis, but new evidence suggests that inflammation has been implicated in the pathogenesis of OA.(34) For that reason, we examined the association between RHOA and cancer because inflammation has been shown to have a role in the pathogenesis of cancer.(35) This relationship has not been examined extensively, with the exception of Nüesch et al., who reported excess cancer mortality among adults with OA compared with the general population.(4) In our study, RHOA was not associated with a significantly higher risk of cancer, although the magnitude of the association (hazard ratio) was comparable to all-cause mortality.

We were interested in determining whether RHOA increased the risk of GI disease mortality because we know that NSAIDs are used to reduce pain and inflammation in adults with hip OA, but may lead to gastrointestinal bleeding and an increased risk of GI disease mortality. (36, 37) We did not find a significant association between RHOA and GI disease mortality; however, the magnitude of the increased risk (25%) of GI disease mortality among women with RHOA was similar to that of CVD mortality. The lack of statistical power was also evident in the Nüesch et al. study, which reported a non-significant 47% higher excess GI disease mortality among adults with OA.(4) Additional studies or a meta-analysis might provide more definitive examination of this association.

We performed 2 sensitivity analyses. The first (THR) showed that the effect of RHOA (Croft 2) on all mortality outcomes was more robust (increase in HR; range: 4.8% to 10.7%) and the risk of cancer mortality was significant when sensitivity analyses were performed excluding women who had undergone THR. In addition, women with and without THR did not vary by demographic or medical characteristics (data not shown). This suggests that THR may have protective long-term effects on mortality, and other longitudinal studies support this hypothesis.(23, 24) The second sensitivity analysis found only a modest effect of using different case definitions of RHOA. RHOA (defined using K/L 2) was significantly associated with CVD mortality, but not all-cause mortality. With the

exception of GI disease mortality (49% increased risk in women with RHOA), the association between RHOA (K/L 2) and mortality outcomes was less robust compared with RHOA (Croft 2), possibly as a result of low statistical power (3.5% and 7.4% had RHOA [K/L 2] at baseline and year 8, respectively).

Our study has several limitations. First, our findings are not generalizable to nonwhite women, younger women, or to men. Second, the internal validity of the study may have been subject to selection bias, because the 15% of women who did not have radiographs at baseline were shown to have poorer health characteristics than women included in the analysis. Nonetheless, not including these women in our analysis likely resulted in our findings being biased to the null, because they were significantly more likely to die during our study period. Third, although we accounted for many covariates, residual confounding due to unmeasured phenomena is a potential feature of every observational study. For instance, we did not have information on cholesterol, hypertension, vitamin D, or statin use at baseline and year 8. Nonetheless, a sensitivity analysis using only baseline observations found that adjusting for measured hypertension in addition to all the multivariate characteristics (data not shown) did not attenuate the association between RHOA (all 3 definitions) and all-cause and CVD mortality. Finally, there was limited statistical power to examine the association between symptomatic OA and mortality because <3% of women had this condition.

Our study has several strengths. First, a large sample (7889 participants) was used from a population-based cohort study that had valid hip radiographs at baseline, making this the largest prospective study on OA and mortality. Second, some changes in hip OA status over time (no hip OA to hip OA) can be accounted for, though not completely, because measurements for hip OA were available at baseline and year 8. Third, RHOA and mortality were confirmed objectively. Fourth, we controlled for many confounders that may explain the association between OA and mortality. Finally, our disease-specific mortality models accounted for competing risks of mortality, and as a result, addressed non-informative censoring.

In conclusion, RHOA was associated with an increased risk of all-cause and specifically CVD mortality in older white women independent of the many other risk factors examined. Physical function explained about 43% and 25% of the increased risk of all-cause and CVD mortality in women with RHOA. Efforts to reduce morbidity and possibly mortality among adults with RHOA might benefit by expanding the use of standard, recommended interventions for arthritis, including physical activity and self-management interventions available in the community and clinical centers. These evidence-based interventions have been shown to improve function and health status, and reduce pain, factors known to be associated with mortality.(27–29, 38, 39) A primary public health concern is the reduction of morbidity, in addition to mortality, and community-delivered evidence-based interventions are 1 way to address tertiary prevention in populations substantially affected by the sequelae of osteoarthritis.

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Figure 1.
Flow chart showing participants from baseline to year 8 for the Study of Osteoporotic Fractures.

Characteristics of women with and without radiographs and by radiographic hip osteoarthritis (RHOA)tatus^a at baseline (1986–1988)^b

Table 1

Characteristic	Radiographs at Baseline			RHOA (Croft 2)		
	Without (n=1815) ^c	With (n=7889) ^c	P Value	Yes (n=635) ^c	No (n=7254) ^c	P value
Age, y, mean (SD)	73.6 (6.2)	71.4 (5.1)	<.01	72.7 (5.3)	71.2 (5.0)	<.01
Education >12 y	33.6	38.4	<.01	37.5	38.2	.72
BMI, kg/m ² , mean (SD)	26.5 (5.0)	26.5 (4.6)	.88	26.7 (4.6)	26.5 (4.6)	.36
Current smoker	11.1	9.7	.08	8.5	9.8	.29
Health (fair/poor/very poor)	21.8	15.7	<.01	20.5	15.3	<.01
Diabetes	9.0	6.6	<.01	8.5	6.4	.04
Stroke	4.7	2.6	<.01	1.6	2.7	.09
COPD	11.5	8.7	<.01	8.3	8.8	.73
Osteoporosis	17.7	14.1	<.01	15.7	14.0	.22
Previous fracture since age 50	42.8	35.8	<.01	37.4	35.6	.38
Calcium use						
Never	51.5	48.9	.07	49.1	48.9	.94
Past	7.3	8.1		8.0	8.1	
Current	41.2	43.0		42.9	43.0	
Estrogen use						
Never	63.2	57.7	<.01	60.5	57.4	.08
Past	25.1	27.9		27.0	28.0	
Current	11.7	14.4		12.5	14.6	
Physical activity (kcal/wk), mean (SD)	445 (591)	592 (678)	<.01	504 (629)	600 (681)	<.01
Physical function, m/s, mean (SD)	0.97 (0.24)	1.03 (0.21)	<.01	0.97 (0.23)	1.03 (0.21)	<.01
Disability, IADLs, mean (SD)	0.95 (1.30)	0.59 (1.04)	<.01	0.82 (1.19)	0.56 (1.03)	<.01
Hip Pain	37.7%	35.4%	.10	46.7%	34.5%	<.01
NSAID use	5.2	4.8	.47	6.0	4.7	.14
Died	75.0	67.7	<.01	74.5	67.2	<.01

Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; IADLs, instrumental activities of daily living.

^a RHOA status determined by a Croft score 2.

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Data from the Study of Osteoporotic Fractures, a US population-based cohort study of 9704 white women aged 65 years with a mean follow-up of 16 years.

All values in this column are percentages unless otherwise indicated

Table 2

Adjusted and unadjusted risk of all-cause and disease-specific mortality associated with radiographic hip osteoarthritis (RHOA)^a

RHOA Diagnosis Criterion	All-Cause HR (95% CI)	CVD HR (95% CI)	Cancer HR (95% CI)	GI Disease HR (95% CI)	All Other Causes HR (95% CI)
Croft 2^b					
Unadjusted	1.28 (1.18, 1.39)	1.43 (1.26, 1.63)	1.19 (0.97, 1.47)	1.34 (0.83, 2.17)	1.18 (1.03, 1.34)
Age-adjusted	1.17 (1.08, 1.28)	1.29 (1.13, 1.46)	1.16 (0.95, 1.43)	1.22 (0.75, 1.97)	1.07 (0.94, 1.23)
MV ^c	1.14 (1.05, 1.24)	1.24 (1.09, 1.41)	1.18 (0.96, 1.45)	1.25 (0.77, 2.03)	1.03 (0.90, 1.18)
Croft 2^b excluding THR					
Unadjusted	1.39 (1.27, 1.51)	1.52 (1.33, 1.74)	1.32 (1.07, 1.64)	1.49 (0.90, 2.47)	1.29 (1.12, 1.48)
Age-adjusted	1.27 (1.16, 1.39)	1.36 (1.19, 1.55)	1.29 (1.04, 1.59)	1.34 (0.81, 2.23)	1.18 (1.02, 1.35)
MV ^c	1.24 (1.13, 1.35)	1.30 (1.14, 1.50)	1.30 (1.05, 1.61)	1.36 (0.82, 2.27)	1.14 (0.98, 1.31)
K/L 2^d					
Unadjusted	1.30 (1.17, 1.44)	1.51 (1.29, 1.77)	1.00 (0.75, 1.33)	1.72 (0.99, 2.99)	1.20 (1.02, 1.42)
Age-adjusted	1.12 (1.01, 1.25)	1.26 (1.08, 1.48)	0.96 (0.72, 1.27)	1.47 (0.84, 2.55)	1.03 (0.87, 1.22)
MV ^c	1.10 (0.99, 1.22)	1.24 (1.05, 1.45)	0.96 (0.72, 1.28)	1.49 (0.85, 2.59)	1.00 (0.84, 1.19)

Abbreviations: CVD, cardiovascular disease; GI, gastrointestinal; HR, hazard ratio; CI, confidence interval; THR, total hip replacement.

^aData from the Study of Osteoporotic Fractures, a US population-based cohort study of 9704 white women aged 65 years with a mean follow-up of 16 years. All disease-specific mortality models accounted for competing risks of mortality.

^bAt least 1 hip with definite joint space narrowing (JSN) or osteophytes plus 1 other radiographic feature.

^cMultivariate models adjusted for age, body mass index, education, smoking, health status, diabetes, and stroke. These potential confounders met at least 1 the following 2 criteria: 1) associated with RHOA at α .05, or 2) shown to be associated with mortality in the scientific literature. Time-varying covariates not ascertained at baseline and year 8 could not be considered for inclusion in multivariate models.

^dAt least 1 hip with definite JSN and osteophytes.

Table 3

Mediation analysis using marginal structural modeling to estimate the indirect effect^a of radiographic hip osteoarthritis (RHOA^b) on all-cause and CVD mortality^{c, d}

Mediating Variable	All-Cause HR (95% CI)	P	Mediation Effect ^e	CVD HR (95% CI)	P	Mediation Effect ^e
Physical activity	1.01 (0.97–1.05)	.56	7.1	1.00 (0.95–1.07)	.75	0
Physical function	1.06 (1.02–1.10)	<.01	42.9	1.06 (1.00–1.13)	.07	25.0
Disability	1.02 (0.98–1.05)	.46	13.3	1.01 (0.95–1.08)	.66	4.2
Hip Pain	1.00 (0.96–1.03)	.79	0	1.00 (0.94–1.06)	.99	0
NSAID use	1.00 (0.96–1.04)	.86	0	1.00 (0.94–1.06)	.90	0

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug

^aThe indirect effect is a measure of the amount of mediation for each variable individually in the causal pathway between RHOA and the mortality outcomes controlling for all potential confounders

^bRHOA status determined by a Croft score 2. At least 1 hip with definite joint space narrowing or osteophytes plus 1 other radiographic feature.

^cData from the Study of Osteoporotic Fractures, a US population-based cohort study of 9704 white women aged 65 years with a mean follow-up of 16 years. CVD mortality model accounted for competing risks of mortality.

^dAll 5 mediation analyses adjusted for age, body mass index, education, smoking, health status, diabetes, and stroke.

^ePercent of the association between RHOA and mortality that can be explained by the mediator= (HR_{indirect effect}/HR_{total effect})*100. HR_{total effect}=1.14 for all-cause mortality and 1.24 for CVD mortality