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Hip Symptoms are Associated with Premature Mortality: The Johnston County Osteoarthritis Project

Rebecca J. Cleveland, PhD[1,2], **Carolina Alvarez, MS**[1], **Amanda E. Nelson, MD, MSCR**[1,2], **Todd A. Schwartz, DrPH**[1,3,4], **Jordan B. Renner, MD**[5], **Joanne M. Jordan, MD, MPH**[1,2], **Leigh F. Callahan, PhD**[1,2,6]

[1]Thurston Arthritis Research Center, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

[2]Division of Rheumatology, Allergy and Immunology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

[3]Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA

[4]School of Nursing, University of North Carolina, Chapel Hill, NC, USA

[5]Department of Radiology, University of North Carolina, Chapel Hill, NC, USA

[6]Departments of Orthopaedics and Social Medicine, University of North Carolina, Chapel Hill, NC, USA

Abstract

Objective: To investigate the impact of hip osteoarthritis (OA) and/or hip symptoms on excess mortality.

Design: We analyzed data from 3,919 individuals in a community-based prospective cohort of African Americans and Caucasians age ≥45 years. Women ≥ 50 years of age and all men underwent supine anteroposterior pelvic radiography at baseline, with the participant's feet in 15 degrees of internal rotation. Hip radiographic (rOA) was defined as a Kellgren-Lawrence grade of >2 in at least one hip. Participants completed questionnaires at baseline to determine presence of hip symptoms and covariate status. Participants with symptomatic hip rOA (SxOA) are a subset of individuals with hip rOA and symptoms in the same hip. Multiple imputation was used to impute

Corresponding Author/Request for Reprints: Rebecca J. Cleveland, PhD, Thurston Arthritis Research Center, University of North Carolina, 3300 Thurston Building, Campus Box #7280, Chapel Hill, NC 27599-7280, Phone (919) 966-4533, FAX (919) 966-1739, becki@unc.edu.

AUTHOR CONTRIBUTIONS

1) Conception and design: RJC, AEN, TAS, JMJ, LFC. Acquisition of data: RJC, JBR, JMJ, LFC. Analysis and interpretation of data: RJC, CA, AEN, TAS, LFC.

2) Drafting of the manuscript: RJC, CA, LFC. Critical revisions for important intellectual content: all authors.

3) Final approval of the version submitted: all authors.

4) Rebecca J. Cleveland (becki@unc.edu) and Leigh F. Callahan (leigh_callahan@med.unc.edu) take responsibility for the integrity of the work as a whole, from inception to finished article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this work.

missing values of covariates. Mortality was determined through 2015 and follow-up time was calculated from baseline assessment until death or censoring which took place when a participant was lost to follow-up or reached the end of study period. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals. We carried out additional analyses stratified by sex, race, age and obesity.

Results: Mean follow-up time was 14.2 years during which 1762 deaths occurred. There were 29.9% participants in our population with hip rOA at baseline. Compared to those with neither hip rOA nor hip symptoms, we observed an increased risk of all-cause mortality in participants with hip symptoms alone (HR=1.28, 95% 0=1.13-1.46), but no association for hip rOA either with or without symptoms. In stratified analyses we observed increased associations for hip symptoms alone and hip sxOA in those <65 years (43% and 39% increase, respectively) and in Caucasians (34% and 21% increase, respectively).

Conclusions: Individuals who had hip symptoms without hip rOA had an increased risk of mortality. These effects were particularly strong for those who were <65 years of age and Caucasians. Effective interventions to identify those with hip pain in order to lessen it could reduce premature mortality.

Keywords

Hip osteoarthritis; Joint pain; Mortality; Epidemiology

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder and is commonly found in the hip. Hip OA is often accompanied by pain and stiffness and frequently leads to mobility issues[1]. Further, hip OA can lead to reduced range of motion and muscle strength[2]. As a result, hip OA is a leading cause of functional incapacity and disability in adults.

The functional limitations in those with hip OA can also lead to reduced physical activity which can increase the risk of developing and having more severe comorbid conditions, several of which are associated with premature death, including cardiovascular disease (CVD)[3]. Further, walking disability itself has been shown to be associated with increased mortality[4].

Results from studies focused on hip OA as a risk factor for premature death have been equivocal. In a population of 2927 Italians ≥ 65 years of age who were followed for a mean of 4.4 years, authors reported no association between clinically diagnosed hip OA and increased all-cause mortality (0.96 [0.77-1.20])[5]. However, Barbour et al. found evidence suggesting an increased risk of premature death with hip OA (K-L grade ≥ 2) among older white women ≥ 65 years with 16 years of follow-up (HR=1.10; 95% CI=0.99-1.22)[6]. Finally, another study of Swedish adults ≥ 45 years with a clinical diagnosis of hip OA reported a decreased risk of death after 16 years of follow-up (HR=0.90; 95% CI=0.87, 0.92)[7]. Further, CVD-specific death has been shown to be increased in those with hip OA[6].

Due to the uncertain relationship between hip OA and death, we sought to examine associations between hip OA and both all-cause and CVD-specific death, independent of

comorbidities, in a cohort with up to 25 years of follow-up. Further, we sought to describe these associations according to sex and race.

METHOD

Study Design and Participants

We used data from the Johnston County Osteoarthritis Project (JoCo OA), a community-based prospective cohort study of OA in North Carolina (NC). We have previously described details of the JoCo OA[89], but briefly, individuals from 6 townships in a predominantly rural NC county were recruited. Participants were English-speaking, noninstitutionalized African Americans (AA) or Caucasians who were at least 45 years of age at enrollment. Two enrollment waves occurred, the first from 1991 to 1998, and the second from 2003 to 2004 to replace lost individuals from the first wave (Appendix Figure I). Consent forms were completed by all participants. At baseline and at up to three follow-up time points, radiographs, clinical examinations, and interviewer-administered questionnaires were completed for all participants. All eligible participants for this analysis had at least one evaluable hip radiograph. The JoCo OA has been continually approved by the Institutional Review Boards at the University of North Carolina, Chapel Hill and the Centers for Disease Control and Prevention (CDC) in Atlanta, GA.

Hip symptoms and rOA definitions

Women ≥ 50 years of age and all men underwent supine anteroposterior pelvic radiography at baseline and each follow-up, with the participant's feet in 15 degrees of internal rotation. Women who were less than 50 years of age did not undergo radiography per protocol. Radiographs were read and interpreted by a single bone and joint radiologist (JBR). We previously reported a high inter-rater and intra-rater reliability for this reader (weighted kappa = 0.859 and 0.886, respectively)[10]. Hips were assigned a Kellgren/Lawrence (K-L) grade from 0 to 4[11] and hip radiographic OA (rOA) was defined as having a K-L grade of ≥ 2 in at least one hip. There were a small number of individuals who indicated that they had a hip replacement due to OA (n=32, 0.8% of our sample) and they were also classified as having hip rOA.

Presence of hip symptoms was assessed at baseline using the question "On most days, do you have pain, aching or stiffness in your [right/left] hip?" In our analyses, hip symptoms took precedence over hip rOA. Individuals with both rOA and hip symptoms in the same hip were classified as having symptomatic hip OA (sxOA) and are a subset of those with hip rOA. In order to capture the independent effects of hip rOA and hip symptoms, we created a 4-level variable with mutually exclusive categories for a participant's worst hip. For example, if a participant had only symptoms in one hip and only rOA in the other hip, then that individual would be classified as having hip symptoms alone. This variable included the following categories: 1) neither hip rOA nor symptoms (referent); 2) hip symptoms alone; 3) hip rOA alone; and 4) both hip symptoms and hip rOA.

Covariates

Several relevant covariates were considered in analyses assessing associations between hip rOA and/or symptoms and death. Covariates included age (continuous), birth cohort (by decade), enrollment wave (first or second), sex, race (AA or Caucasian), self-reported education level (<12 years or ≥12 years), self-reports of hip injury (ever/never), at least one knee with rOA (K-L grade ≥ 2), ever alcohol use and ever smoking; and back symptoms (assessed as reporting either lower back trouble or having chronic stiffness or deformity of the back or spine). We defined CVD as self-reports of stroke, circulation problems, heart attack or other heart problems and/or use of CVD-specific medications. Other covariates included obesity (body mass index [BMI, kg/m^2] ≥ 30), meeting the CDC guidelines for moderate/vigorous physical activity (MVPA, yes or no), use of non-steroidal anti-inflammatory drugs (NSAIDS, yes or no), self-reported disability (defined as at least mild disability with a score of ≥1 assessed with the Health Assessment Questionnaire (HAQ)[12]), and self-reports of elevated depressive symptoms (Center for Epidemiologic Studies Depression (CES-D) score of ≥16[13]). Our comorbidity variable used in analyses was defined as reporting at least 1 of 6 of comorbidities (yes or no) including liver disease, diabetes, hypertension, cancer, CVD, or depressive symptoms. Further descriptions of the covariates can be found in the Appendix.

Mortality

At each follow-up time point we assessed the vital status of all participants. Follow-up assessments took place from 1999-2004 (T1), 2006-2010 (T2) and 2013-2015 (T3). Individuals not known to be alive (died, moved out of the area or lost to follow-up) after the T3 follow-up was completed were submitted to the National Death Index (NDI) to ascertain vital status, date and cause of death through December 31, 2015. Known deaths not found through NDI records but confirmed through local vital records searches were included. Using the International Classification of Diseases (ICD), CVD deaths were based on ICD-9 codes 393 to 398 and ICD-10 codes I-00 to I-99 listed on the death certificate as the underlying cause of death.

Statistical analysis

We calculated descriptive statistics for covariates at baseline, presenting continuous variables as means and standard deviations (±SD) and categorical variables as frequencies and percentages. All tests were two-sided and considered statistically significant at the 0.05 level. Analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC).

We were missing covariate information for at least one baseline measure for 8.2% of the participants (Figure I). All baseline variables were used in a multiple imputation (MI) model in order to impute missing baseline covariate values, using logistic regression by fully conditional specification methods (FCS) for binary variables which performs best for missing-at-random patterns and a missing proportion of less than 50%[14]. Ten imputed datasets were generated so that the number of imputations was at least equal to the percent of data missing one or more covariates[15] (for more information see the Appendix). A complete-case sensitivity analysis was also carried out (Appendix Table I, Model 2).

We used Kaplan-Meier methods[16] to generate survival curves by baseline hip rOA and hip symptoms status. We also generated baseline age and sex-adjusted survival curves using inverse probability weights[17]. Cox proportional hazards regression[16] was used to estimate baseline hazard ratios (HR) and corresponding 95% confidence intervals (CI) for all-cause and CVD-specific mortality in relation to hip rOA and hip symptoms. We examined whether the proportional hazards assumption was met using Schoenfeld residuals and testing their correlation with time, time^2 and log(time) from Cox models[16] and found no evidence of violation of this assumption. CVD-specific mortality analyses were modeled using the CVD cause-specific hazard, treating non-CVD mortality competing events as censored observations for all analyses[18]. We conducted separate analyses in each of the 10 imputed datasets, the estimated parameters from all imputed datasets were then synthesized to generate a single estimate according to Rubin's rules[19]. All models were stratified by birth cohort (decade) to account for calendar effects, which is recommended when following healthy people and when the calendar effect is likely to influence mortality, as well as other risk factors[20]. We calculated follow-up time from the baseline assessment until death, or until censoring which took place when a participant was lost to follow-up or reached the end of study period (December 31, 2015). Age was used as the time scale with left truncation for age at study entry.

We conducted pre-specified stratified analyses to describe associations between hip rOA status (rOA and/or hip symptoms) measures and all-cause or CVD-specific survival by each of obesity (BMI<30 or BMI≥30), age group split at the median (< 65 years or ≥ 65 years), race (Caucasian or AA) and sex (male or female).

As our analyses were carried out on a person level, there were some participants who had rOA but no symptoms in one hip and symptoms without rOA in the other hip (n=54, 1.4%). A conservative approach was used where those individuals were included in the hip rOA alone group (i.e., no hip symptoms;7.2% of those classified as hip rOA alone). We carried out additional sensitivity analyses placing those participants in the hip symptoms alone group instead, as well as a sensitivity analysis using groin symptoms as our measure of hip symptoms (having groin pain at clinical hip exam [first enrollment wave]; or indicating that the site of "hip pain/aching/stiffness" is in the groin [second enrollment wave]) (Appendix Table I, Models 3 and 4, respectively). Additional analyses were also conducted using only binary variables for hip rOA (rOA *vs.* no rOA), hip sxOA (sxOA *vs.* no sxOA) and severe hip rOA with a K-L grade ≥3 (severe rOA *vs.* no severe rOA), respectively, results of which are presented in Appendix Table II.

Other Sensitivity analyses:

We carried out six sensitivity analyses in addition to the ones previously described (for 9 in total) (Appendix Table I): to reduce confounding due to pre-existing disease by excluding deaths occurring in the first year of follow-up after baseline (Model 5); to evaluate covariates as they change over time in a model using time-varying covariates (TVC; Model 6a); a model using TVC among participants with ≥ 1 follow-up (Model 6b); a model using TVC among participants with ≥2 follow-ups (Model 6c); to account for generalized pain in a model including 14 other symptomatic joints as covariates, including left and right counts of

shoulders, elbows, wrists, hands, knees, ankles and feet (Model 7); and to assess the effects of severe rOA in a model using a K-L ≥ 3 to define hip rOA instead of K-L ≥ 2 (Model 8).

RESULTS

Baseline characteristics of the JoCo OA cohort (n=3919) are reported in Table I. Mean age was 62.3 years, 61% were female and 33% were African American. At baseline, 45% of participants had neither hip rOA nor symptoms, 19% had hip rOA alone, 25% had hip symptoms alone and 11% had both hip rOA and hip symptoms. The mean follow-up time was 14.2 years through 2015 during which we observed 1762 deaths overall, 661 of which were due to CVD.

Unadjusted and age/sex adjusted Kaplan-Meier survival curves are presented in Figures IIa and IIb, respectively. Unadjusted survival curves (Figure IIa) show those with both hip rOA and symptoms (i.e., hip sxOA) had the worst survival (median 16.1 years), that those with hip symptoms alone and those with hip rOA alone had similar survival (median 18.6 and 18.5 years, respectively), and those with neither hip rOA nor hip symptoms had the best survival (median 22.8 years). However, after adjustment for age and sex (Figure IIb), those with hip sxOA had similar survival to those with hip symptoms alone, and those with hip rOA alone had similar survival to those with neither rOA nor symptoms.

In Table II we present results from Cox proportional hazards models to estimate risk of death due to baseline values of the 4-level combined hip rOA/symptoms variable. In fully adjusted models, compared with having neither hip symptoms nor hip rOA we observed no associations for having hip rOA alone or having hip sxOA. However, we did observe an increased risk of death for those with hip symptoms alone (HR=1.28, 95% CI=1.12-1.46). We observed similar associations when estimating risk of CVD-specific death.

Results from sensitivity analyses are presented in Appendix Table I. These include analyses: a) carried out on a complete-case dataset (Model 2); b) placing discordant joint hip rOA and symptoms in the hip symptoms alone group instead of the hip rOA group (Model 3); c) using groin symptoms instead of hip symptoms (Model 4); d) excluding deaths occurring in the first year of follow-up after baseline (Model 5); e) using time varying covariates (TVC) instead of those measured only at baseline (Models 6a, 6b and 6c); adjusting for 14 other joints with symptoms (Model 7); and f) defining hip rOA as a K-L grade ≥ 3 instead of a K-L ≥ 2 (Model 8). Results from most sensitivity analyses (models 2-6a, 7, 8) did not vary substantially from those found in Model 1 (as taken from Table II, All-cause Mortality Model 3). However, compared to other models, both Models 6b and 6c using TVC showed attenuated risk for hip symptoms when compared to neither hip symptoms nor hip rOA.

Stratified analyses

The results for covariate-adjusted associations between the 4-level combined hip rOA/symptoms variable and all-cause mortality stratified by obesity and demographic variables are presented in Table III. Compared with neither hip rOA nor hip symptoms, estimates for the risk of death for having hip symptoms alone were slightly stronger for men than women. In analyses stratified by age at baseline, those who were <65 years had an increased risk of

death for both hip symptoms alone (HR=1.43, 95% CI=1.19-1.72) and hip sxOA (HR=1.39, 95% CI=1.07-1.81); those ≥ 65 years had no increased risk of death for either hip rOA, hip symptoms or the combination (hip sxOA). Similarly, compared with African Americans, stronger associations were observed among Caucasians for both hip symptoms alone (HR=1.34, 95% CI=1.15-1.57) and hip sxOA (HR=1.21, 95% CI=1.00-1.46). Stratified results for CVD-specific deaths were similar to, but slightly stronger than, those seen for all-cause mortality (Appendix Table III).

DISCUSSION

This is the first report to our knowledge of the association between distinct groups of hip rOA both with and without hip symptoms on premature mortality in a population-based study of African American and Caucasian men and women. We report that individuals with hip symptoms alone are at increased risk of death when compared to individuals with neither hip rOA nor hip symptoms in a cohort of individuals with over 25 years of follow-up. We did not find any increase in death among those with hip rOA alone with the same comparison group overall, although we did find evidence of an increased risk of death for those with hip sxOA in subgroup analyses.

When we expanded our analyses to include time-varying covariates to capture hip rOA and hip symptoms over time, we found similar associations for hip rOA both with and without symptoms as seen in analyses using baseline measures (Appendix Table I, Model 6a). However, when we restricted our analyses to participants with at least 1 or 2 follow-ups, the increased associations for hip symptoms alone in analyses with baseline measures were no longer observed (Appendix Table I, Models 6b and 6c). One explanation may be that in addition to developing hip rOA and pain, individuals are accumulating greater numbers of comorbidities over time. In our study, all comorbidities were associated with increased mortality ranging from HR=1.10 to HR=1.47. Residual confounding is another potential explanation, even though we included those comorbidities in our models. For example, those who did not return for a follow-up were potentially sicker with more comorbidities further attenuating our results. This may suggest that the negative effects of hip rOA are stronger earlier in the disease course or at younger ages before the effect of other comorbidities surpasses any risk from hip rOA. This is suggested by the increased HR observed for hip sxOA in those under the age of 65 (HR=1.39), whereas we observed no increased mortality among those aged 65 or older.

In sub-analyses, our results show no association with excess mortality for those with hip rOA compared to those without hip rOA without accounting for hip symptoms (Appendix Table II). Likewise, when we looked at hip sxOA with a comparison group of no hip sxOA we also observed no association (HR=0.95; 95% CI=0.83-1.10). This is in contrast to results reported by Turkiewicz, et al., who reported a decreased risk of death using Swedish registry data based on an ICD-10 diagnostic code (HR=0.90; 95% CI=0.87, 0.92)[7]. Differences may be due to that study using healthcare data which is subject to finding more cases of hip OA and/or pain since individuals in those types of studies tend to seek out medical care. However, in both the analyses by Turkiewicz, et al. and our sub-analyses of sxOA, the referent group included participants with hip rOA who either did not report (in JoCo OA) or

seek care (in Swedish registry) for hip pain. In contrast, two other international studies reported increased associations for hip OA. One small study of clinically diagnosed symptomatic hip OA reported an increased risk of death among a Dutch sample of sibling pairs in univariate analyses, but results were greatly attenuated when adjustments were made for age and sex[21]. Another Italian study whose definition of hip OA was based on a mixture of radiographs and symptoms also did not find an association with mortality[5]. Traditional meta-analyses also report no increased risk for hip OA[522]. However, an individual patient data (IPD) meta-analysis from several international cohorts, including JoCo OA, was conducted and found the associations between hip pain and death were stronger among US cohorts[23]. Further, a study by Barbour et al. reported an increased risk of death among a sample limited to older women in the US with hip rOA, although this analysis did not take hip pain into consideration[6].

A possible explanation for the discordant findings is that the symptoms of hip OA do not always correlate with radiographic and pathologic features[24]. Several conditions may lead to hip pain including comorbidities, injury and referred back pain. It is possible that those with hip rOA, but without pain, have less disability than those who do have hip pain, and disability has been shown to be associated with increased mortality[25]. In our study it is suggested that hip symptoms, not hip rOA, are associated with excess mortality. Other studies have also suggested that pain may be the main driver of excess disability and mortality, and there is a large and growing body of literature focused on pain and mortality[2627]. The impact that disability resulting from joint pain has on mortality is supported by research showing that OA accounts for a large portion of the years lived with disability and quality-adjusted life-years lost[28]. However, when we took presence of pain occurring in 14 additional joints into account in sensitivity analyses, results were largely unchanged (Appendix Table I, Model 7). Further, since our data are population-based and not based on healthcare data we may not be capturing individuals with the most severe pain and hip rOA. While it seems logical that individuals who seek out medical care for their joint pain may have more severe disease and therefore suffer from an increased risk of death, this does not seem to be the case in studies using healthcare data. This is potentially due to individuals presenting in the healthcare system who suffer from increased comorbidities overall, therefore diluting the effects seen for hip OA.

Many shared risk factors exist between CVD and OA, and it has been suggested that these conditions have overlapping causal pathways[29]. CVD has also been suggested as an important source of morbidity in those with OA, with previous studies reporting more CVD in those with OA[3031]. However, our results for CVD-specific mortality were similar to those seen for all-cause death. This may be due to the fact that over a third of the deaths in our cohort are CVD-related (38%).

We acknowledge that measuring comorbidities at one point in time (baseline) may not adequately capture disease burden in a longitudinal cohort with a long follow-up. For example, in our cohort, obesity increased from 40% at baseline to 49% at 3rd follow-up, while CVD increased from 22% at baseline to nearly 48% at the 3rd follow-up, and high blood pressure increased from 40% to 84%. It has been reported that in the US, between 30 and 47% of people with heart disease, diabetes, and obesity report having been diagnosed

with arthritis by a doctor[32]. However, our comorbidity variable used in analyses was defined as having any of 6 self-reported conditions so we did not assess the effect of any single individual condition in models. But in time-varying models, having hip symptoms alone was associated with death even after accounting for increased comorbidities over time (Appendix Table I, Models 6a, 6b and 6c). This may be due to increased disability associated with pain, where disability has been shown to be associated with death, poor health outcomes and comorbidities[2530]. However, in these analyses we also observed that the risk of death associated with hip symptoms decreased when limiting analyses to participants with more follow-up assessments. This is likely due to differential attrition, where those who were lost to follow-up over time were more likely to be in poor health, with more comorbidities, and were therefore unable to provide hip rOA or hip symptoms data at further follow up time points.

Limitations include that we were not able to assess how long a participant had hip rOA prior to study entry, nor were we able to capture incident cases in real time, but only able to determine case status at follow-up assessments with intervening periods of time which varied in duration. However, our TVC models included a counting process in the Cox proportional hazards regression model which assumes participants are at the same risk of the event until the end of the follow-up period[16]. The measure of hip symptoms was also somewhat crude being defined as having mild or greater hip symptoms on most days. However, when we additionally included low back symptoms in the model to account for referred hip symptoms, the results did not change, nor did they change meaningfully when we used groin symptoms instead of hip symptoms (Appendix Table I, Model 3). As happens in most longitudinal studies, there was some study attrition. While we were able to obtain death status on participants whether or not they returned, the same is not true for our predictor (hip symptoms/rOA) and covariates. This is supported by our sensitivity analyses which used TVC as predictors of death and found results somewhat weaker than those using baseline measures (Appendix Table I, Models 6a, 6b and 6c).

Strengths include using data from a large community-based cohort of African American and Caucasian men and women with a long follow-up time of 25 years and having up to three follow-up assessments. Our measure of hip OA was radiographically confirmed and read by the same radiologist with high reliability. Further, we collected data on several comorbid conditions as well as lifestyle factors including BMI, physical activity, smoking/alcohol/NSAID use and adjusted for those in analyses which offers an advantage over other analyses which only adjusted for a limited number and type of covariates[721]. Further, we were able to use the data from the multiple time-points to analyze hip symptoms and/or rOA changes over time. Moreover, we also performed several sensitivity analyses to support our results.

While we were unable to confirm associations between hip rOA alone and death in the entire cohort, stratified analyses suggest increased risks for painful hip rOA among Caucasians and those under the age of 65 at baseline. However, our results suggest a moderately increased risk of death among individuals with hip symptoms alone which, along with hip rOA plus symptoms, is a strong predictor of disability, which in turn is a predictor of death[4]. Our results suggest that a focus on reducing pain and preserving function may have a role in attenuating the increased premature death observed among those with hip symptoms.

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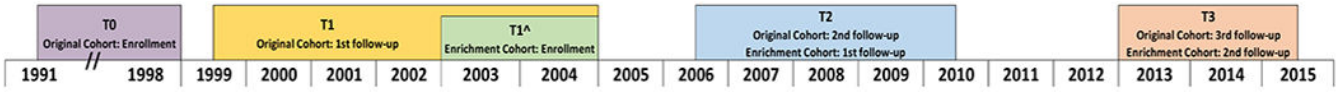
ROLE OF THE FUNDING SOURCE

The funding sources had no direct role in the conduct of the study, data analysis, interpretation of data or in the decision to submit for publication.

Appendix



Appendix Figure I.
JoCoOA Timeline

Appendix Table I.

Adjusted[a] sensitivity analyses in comparison manuscript Table II All-cause Mortality results from Model 2[b]

		Neither Hip rOA nor Symptoms	Hip rOA Only	Hip Symptoms Only	Both Hip rOA and Hip Symptoms
Model 1	Manuscript Table II, Model 3	Ref.	1.06 (0.93, 1.20)	**1.28 (1.13, 1.46)**	1.06 (0.91, 1.24)
Model 2	Complete-case analysis (n=3604)	Ref.	1.06 (0.92, 1.21)	**1.27 (1.11, 1.46)**	1.03 (0.87, 1.22)
Model 3	Discordant hips with rOA/ symptoms placed in Hip Symptoms Only group	Ref.	1.04 (0.91, 1.19)	**1.28 (1.13, 1.45)**	1.06 (0.91, 1.25)
Model 4	Groin symptoms replacing hip symptoms	Ref.	1.00 (0.89, 1.11)	**1.20 (1.01, 1.43)**	0.91 (0.73, 1.14)
Model 5	Excluding participants with deaths in the 1st year of follow-up after baseline	Ref.	1.05 (0.93, 1.20)	**1.29 (1.13, 1.47)**	1.07 (0.91, 1.26)
Model 6a[c]	Using TVCs	Ref.	1.02 (0.90, 1.16)	**1.32 (1.15, 1.51)**	0.96 (0.82, 1.12)
Model 6b[c]	Using TVCs; only participants with 2 or more time points (base + 1 FU, n=2349)	Ref.	0.97 (0.81, 1.16)	1.15 (0.93, 1.42)	0.96 (0.76, 1.21)
Model 6c[c]	Using TVCs; only participants with 3 or more time points (base + 2 FU, n=1322)	Ref.	0.96 (0.69, 1.31)	1.15 (0.76, 1.75)	1.24 (0.82, 1.88)

		Neither Hip rOA nor Symptoms	Hip rOA Only	Hip Symptoms Only	Both Hip rOA and Hip Symptoms
Model 7	Adjusting for 14 other joints with symptoms[d]	Ref.	1.05 (0.92, 1.19)	**1.25 (1.09, 1.42)**	1.03 (0.88, 1.21)
Model 8	K-L ≥ 3 as severe rOA variable	Ref.	1.01 (0.75, 1.36)	**1.19 (1.06, 1.33)**	0.98 (0.68, 1.40)

[a]Adjusted for enrollment wave, age, sex, race, education, hip injury, non-steroidal anti-inflammatory drugs, smoking, alcohol use, physical activity, disability, any of 6 comorbidities, BMI, low back pain.

[b]Data used are multiply imputed (n=10) to estimate missing baseline values for covariates. Stratified over five birth decade cohorts, using age as the time scale, and baseline age for left truncation.

[c]TVC=Time varying covariates; models with TVCs do not include left truncation and use time from baseline as the time scale

[d]Joints include left and right counts of shoulders, elbows, wrists, hands, knees, ankles and feet

Appendix Table II.

Hazard ratios for the association between hip rOA, hip sxOA and severe hip rOA at baseline and all-cause and CVD cause-specific mortality, JoCo OA[a]

	No hip rOA	Hip rOA HR (95% CI)	No hip sxOA	Hip sxOA HR (95% CI)	No Severe Hip rOA	Severe Hip rOA HR (95% CI)
Cohort	**N=2749**	**N=1170**	**N=3504**	**N=415**	**N=3796**	**N=123**
All-cause Mortality						
Number of Deaths	n=1132	n=630	n=1517	n=245	n=1681	n=81
Model 1[b]	ref.	0.98 (0.88-1.08)	ref.	1.08 (0.94-1.24)	ref.	1.02 (0.81-1.28)
Model 2[c]	ref.	0.97 (0.88-1.08)	ref.	1.07 (0.93-1.23)	ref.	0.99 (0.79-1.25)
Model 3[d]	ref.	0.96 (0.87-1.06)	ref.	0.95 (0.83-1.10)	ref.	0.93 (0.74-1.17)
CVD, specific Mortality						
Number of Deaths	n=430	n=231	n=567	n=94	n=634	n=27
Model 1[b]	ref.	0.88 (0.75-1.04)	ref.	1.04 (0.83-1.30)	ref.	0.81 (0.55-1.20)
Model 2[c]	ref.	0.88 (0.75-1.04)	ref.	1.01 (0.81-1.27)	ref.	0.79 (0.53-1.17)
Model 3[d]	ref.	0.85 (0.72-1.01)	ref.	0.88 (0.70-1.11)	ref.	0.73 (0.49-1.08)

[a]Data used are multiply imputed (n=10) to estimate missing baseline values for covariates. Stratified over five birth decade cohorts, using age as the time scale, and baseline age for left truncation

[b]Unadjusted

[c]Adjusted for enrollment wave, sex, race, education

[d]Adjusted for enrollment wave, sex, race, education, hip injury, non-steroidal anti-inflammatory drugs, smoking, alcohol use, physical activity, disability, any of 6 comorbidities, BMI and low back pain

rOA=radiographic osteoarthritis; SxOA=symptomatic rOA; severe rOA=rOA with a KL grade ≥3

Appendix Table III.

Adjusted hazard ratios[a] for the association between hip OA and hip symptoms at baseline and ***CVD-specific mortality***, JoCo OA[b]

Cohort	Neither hip rOA nor symptoms N=1776	Hip rOA without symptoms HR (95% CI) N=755	Hip symptoms without rOA HR (95% CI) N=973	Both hip rOA and symptoms HR (95% CI) N=415
Sex				
Number of Deaths	n=119	n=89	n=111	n=63
Women (n=2395)	ref.	1.11 (0.84-1.47)	**1.41 (1.08-1.86)**	1.10 (0.79-1.51)
Number of Deaths	n=124	n=48	n=76	n=31
Men (n=1524)	ref.	0.81 (0.58-1.13)	**1.47 (1.09-1.97)**	0.90 (0.60-1.36)
Race				
Number of Deaths	n=93	n=41	n=59	n=27
African American (n=1295)	ref.	0.80 (0.55-1.16)	1.26 (0.90-1.77)	**0.63 (0.41-0.99)**
Number of Deaths	n=150	n=96	n=128	n=67
Caucasian (n=2624)	ref.	1.08 (0.83-1.40)	**1.53 (1.19-1.97)**	1.29 (0.95-1.75)
Age				
Number of Deaths	n=75	n=30	n=77	n=26
< 65 at baseline (n=2439)	ref.	1.13 (0.74-1.72)	**1.82 (1.31-2.53)**	**1.69 (1.07-2.67)**
Number of Deaths	n=168	n=107	n=110	n=68
≥ 65 at baseline (n=1480)	ref.	0.89 (0.70-1.14)	1.24 (0.96-1.60)	0.83 (0.62-1.12)
Obesity				
Number of Deaths	n=156	n=94	n=109	n=47
BMI < 30 (n=2354)	ref.	1.04 (0.80-1.34)	**1.56 (1.20-2.02)**	0.93 (0.65-1.31)
Number of Deaths	n=87	n=43	n=78	n=47
BMI > 30 (n=1565)	ref.	0.87 (0.60-1.25)	1.25 (0.91-1.72)	1.09 (0.75-1.58)

[a]Adjusted for enrollment wave, age, sex, race, education, hip injury, non-steroidal anti-inflammatory drugs, smoking, alcohol use, physical activity, disability, any of 6 comorbidities, BMI, low back pain

[b]Data used are multiply imputed (n=10) to estimate missing baseline values for covariates. Stratified over five birth decade cohorts, using age as the time scale, and baseline age for left truncation.

rOA=radiographic osteoarthritis

Appendix Table IV.

Missing values at baseline

Characteristics	Study Visit Baseline (n=3919) n	%
Education	12	0.3
BMI	12	0.3
Physical activity	113	2.9

Characteristics	Study Visit Baseline (n=3919)	
	n	%
Smoking	84	2.1
Alcohol use	83	2.1
Hip injury	40	1.0
NSAID use	45	1.1
Depressive symptoms	61	1.6
Disability	54	1.4
Cancer	5	0.1
CVD	6	0.2
Diabetes	5	0.1
High blood pressure	9	0.2
Liver disease	6	0.2

Multiple Imputation Procedures

The full sample consisted of 3919 participants but were complete for only 3588 (91.6%) participants considering baseline variables of interest. We give the extent and distribution of missing data in Figure I. We used the multiple imputation procedure in SAS statistical software (PROC MI) to impute the relevant missing covariates at baseline and used the last observation carried forward for the lower proportion (<5%) of covariates missing at follow-ups. Variables included in the imputation models consisted of all relevant characteristics listed in the manuscript Table I as well as those detailing the mortality event and its corresponding time-to-event. Ten imputed datasets were created with 20 burn-in iterations before each imputation. MI was conducted by fully conditional specification (FCS) logistic methods for the majority of covariates, which were binary, and using FCS regression for the one continuous variable (BMI, for which normality was ascertained). FCS was used because it performs well for assumptions under MAR and missing proportions lower than 0.5 (our proportion is well below that at 0.08) [http://www2.sas.com/proceedings/sugi30/113-30.pdf].

Objectively Measured Variables

Age: Age in years calculated from birth date to clinic date

Enrollment wave: Enrolled in original cohort (1991-1998) or in new enrollment (2003-2004)

Birth cohort: Cohort in 10-year increments

Sex: Male or female

Knee rOA: Radiographic knee OA, defined as a Kellgren-Lawrence grade of ≥2

Hip rOA: Radiographic hip OA, defined as a Kellgren-Lawrence grade of ≥2

Body mass index: kg/m^2, calculated using clinically measured height and weight

Self-reported Variables

Race: Self-described ethnicity, African American or Caucasian

Education: Self-reported educational attainment, < high school diploma or ≥ high school diploma

Ever smoker: Affirmative for, "Have you EVER smoked at least 100 cigarettes (or 5 packs) in your entire life?"

Ever drinker: Affirmative for, "Have you EVER consumed alcoholic beverages?"

Comorbidities (6):

- Depressive symptoms: Center for Epidemiologic Studies Depression Scale (CES-D), categorized at <16 (no depression) and ≥16 (has depression)[1].

Comorbidities that are affirmative for, "Has a doctor, nurse or other health professional told you that you now have, or have ever had…?":

- Cancer
- Chronic gallbladder/liver trouble
- High blood pressure (hypertension)
- Diabetes or high blood sugar
- Cardiovascular disease: an affirmative response to a) heart attack, b) other heart trouble, c) stroke, d) circulation problems, and/or e) taking CVD-specific medications

Hip symptoms:

Affirmative for, "On MOST days, do you have pain, aching, or stiffness in your LEFT/RIGHT HIP?"

Hip injury, affirmative for either:

- "Have you ever injured your LEFT/RIGHT HIP?"
- "Has a doctor ever told you that you had broken or fractured your LEFT HIP?"

Groin pain:

During the clinical hip exam, the participant indicating having pain in the right and/or left groin

Back pain:

Either:

- Responding “Lower back” to the question “Which joints give you trouble?”
- Responding either “Have now for 6 months or less” or “Have now for more than 6 months” to the question “Has a doctor, nurse or health professional told you that you now have, or have ever had chronic stiffness or deformity of the back or spine?”

Moderate or vigorous physical activity (MVPA):

Self report of types, duration and frequency of physical activities. Categorized as meeting the Centers for Disease Control and Prevention’s recommended 75 minutes of vigorous or 150 minutes of moderate physical activity per week.

Non-steroidal anti-inflammatory drug (NSAID) use:

Open-ended self-report of NSAID medications, for example aspirin, ibuprofen, naproxen and celecoxib

Disability:

Self-reported Health Assessment Questionnaire (HAQ). Disability was defined as having at least mild disability as evaluated with a HAQ score of ≥1[2].

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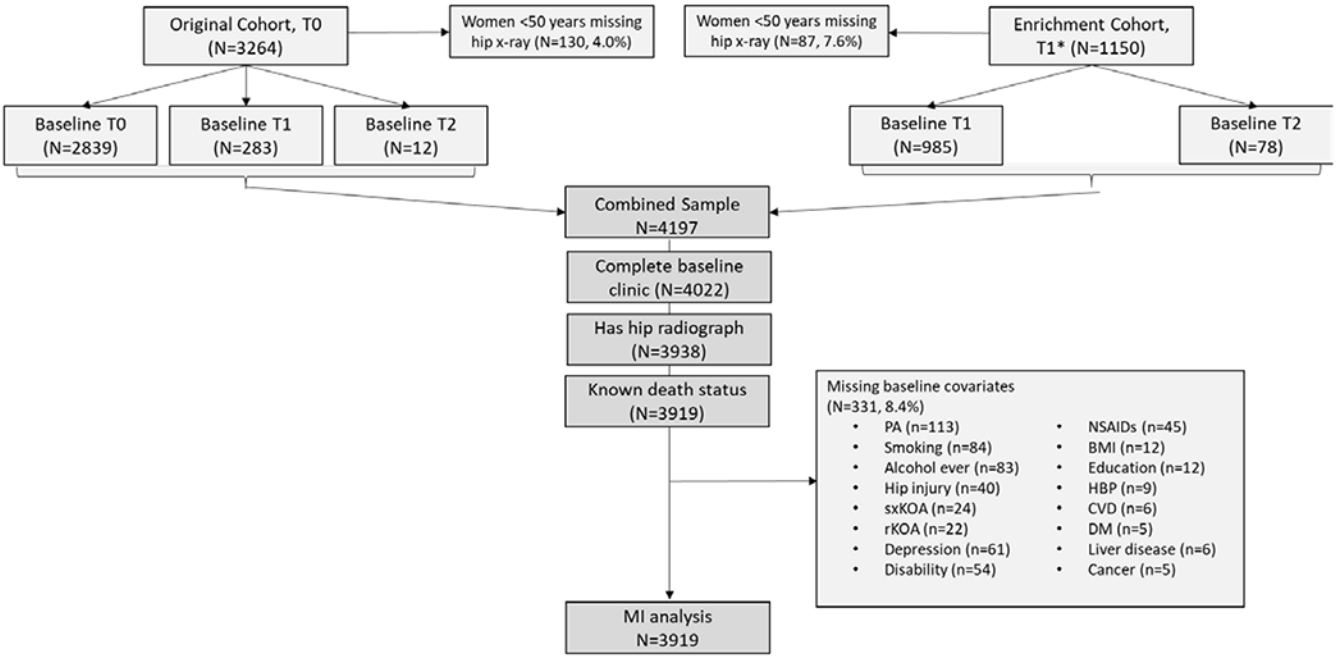

Figure I.

Johnston County Osteoarthritis Study – Baseline Hip rOA participants

Note: rOA=radiographic osteoarthritis; sxOA=symptomatic rOA; MI=multiple imputation; MVPA=moderate/vigorous physical activity; NSAIDs=non-steroidal anti-inflammatory drugs; CVD=cardiovascular disease.

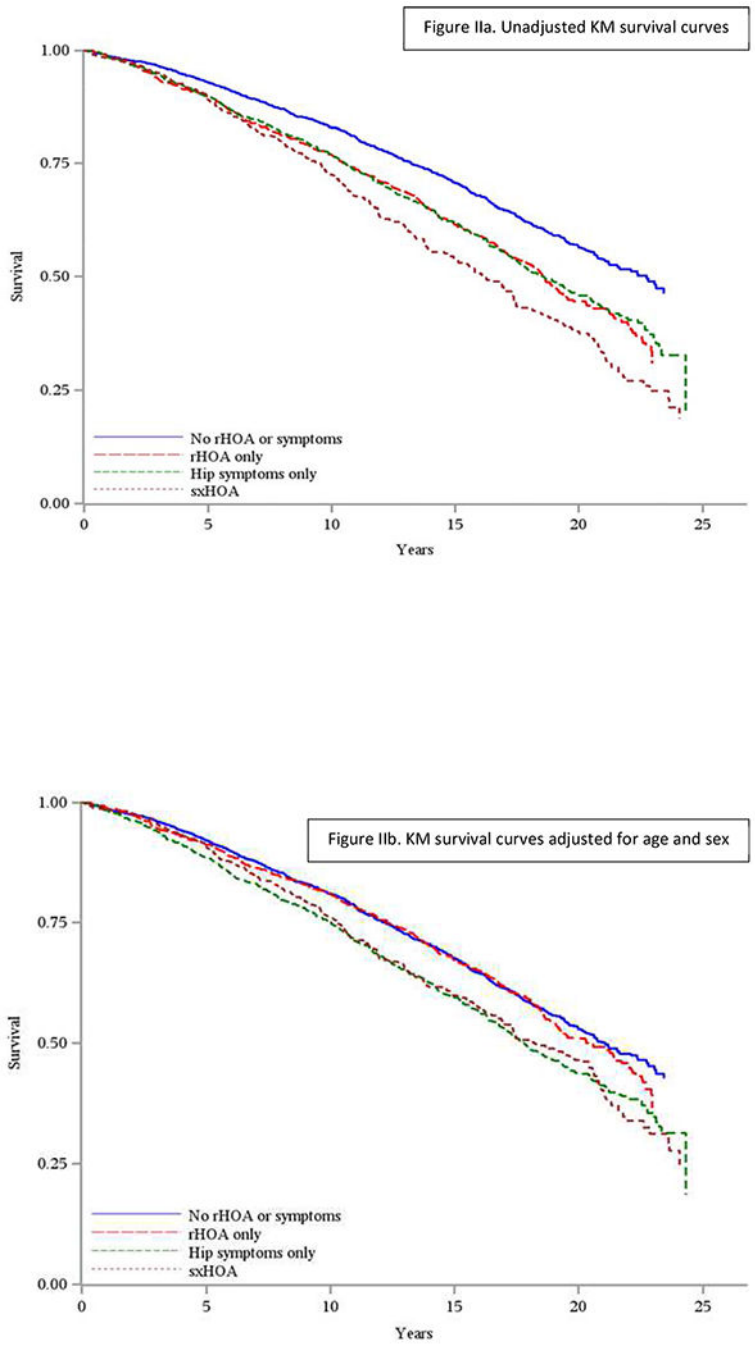

Figure II.

Kaplan, Meier survival curves for mortality by baseline hip rOA and/or hip pain group, unadjusted (a) and adjusted for age and sex (b)

Table I.

Baseline demographic characteristics, the Johnston County Osteoarthritis Project

	Baseline (n=3919) n (%) or mean (SD; range)
Demographics at Baseline	
Enrollment wave	
First (1991-1997)	3015 (76.9%)
Second (2003-2004)	904 (23.1%)
Baseline to follow-up (years)	14.2 (5.9; 0-24.6)
Age at visit (years)	62.3 (9.9; 44.6-93.6)
Female	2395 (61.1%)
African American	1295 (33.0%)
<12 years Education	1442 (36.8%)
BMI (kg/m^2)	30.1 (4.4; 15.1-78.1)
Ever Smoker	1930 (49.2%)
Ever Alcohol use	1809 (46.2%)
<150 MVPA mins/week	3231 (82.4%)
NSAID use	1414 (36.1%)
Self-reported comorbidities	
Cancer	54 (1.4%)
Cardiovascular disease	861 (22.0%)
Hypertension	1563 (39.9%)
Diabetes	539 (13.8%)
Depression	465 (11.9%)
Liver disease	63 (1.6%)
Any of 6 comorbidities above	2292 (58.5%)
Disability	664 (16.9%)
Hip injury	250 (6.4%)
Low back pain	1808 (46.1%)
Hip rOA/Symptoms Variables	
No Hip rOA & No Hip Symptoms	1776 (45.3%)
Hip rOA Alone (No Hip Symptoms)	755 (19.3%)
Hip Symptoms Alone (No Hip rOA)	973 (24.8%)
Hip rOA & Hip Symptoms (SxOA)	415 (10.6%)

BMI=body mass index; MVPA=moderate/vigorous physical activity; NSAID=non-steroidal anti-inflammatory drugs; rOA=radiographic osteoarthritis; SxOA=symptomatic rOA.

Table II.

Hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the association between hip rOA and hip symptoms at baseline and all-cause and CVD cause-specific mortality, J the Johnston County Osteoarthritis Project[a]

Cohort	Neither hip rOA nor symptoms N=1776	Hip rOA without symptoms HR (95% CI) N=755	Hip symptoms without rOA HR (95% CI) N=973	Both hip rOA and symptoms HR (95% CI) N=415
All-cause Mortality				
Number of Deaths	n=665	n=385	n=467	n=245
Model 1[b]	ref.	1.03 (0.91, 1.18)	**1.33 (1.18, 1.49)**	**1.18 (1.02, 1.37)**
Model 2[c]	ref.	1.05 (0.92, 1.19)	**1.37 (1.22, 1.55)**	**1.18 (1.02, 1.37)**
Model 3[d]	ref.	1.06 (0.93, 1.20)	**1.28 (1.13, 1.46)**	1.06 (0.91, 1.24)
CVD-specific Mortality				
Number of Deaths	n=243	n=137	n=187	n=94
Model 1[b]	ref.	0.95 (0.77, 1.18)	**1.45 (1.20, 1.76)**	1.14 (0.89, 1.45)
Model 2[c]	ref.	0.97 (0.79, 1.20)	**1.50 (1.24, 1.82)**	1.13 (0.89, 1.45)
Model 3[d]	ref.	0.97 (0.79, 1.21)	**1.43 (1.16, 1.76)**	1.01 (0.78, 1.31)

[a]Data used are multiply imputed (n=10) to estimate missing baseline values for covariates. Stratified over five birth decade cohorts, using age as the time scale, and baseline age for left truncation

[b]Unadjusted

[c]Adjusted for age, enrollment wave, sex, race, education

[d]Adjusted for age, enrollment wave, sex, race, education, hip injury, non-steroidal anti-inflammatory drugs, smoking, alcohol use, physical activity, disability, any of 6 comorbidities, BMI and low back pain

rOA=radiographic osteoarthritis

Table III.

Adjusted hazard ratios[a] (HR) and corresponding 95% confidence intervals (CI) for the association between hip rOA and hip symptoms at baseline and ***all-cause mortality,*** the Johnston County Osteoarthritis Project [b]

	Neither hip rOA nor symptoms	Hip rOA without symptoms HR (95% CI)	Hip symptoms without rOA HR (95% CI)	Both hip rOA and symptoms HR (95% CI)
Cohort	**N=1776**	**N=755**	**N=973**	**N=415**
Sex				
Number of Deaths	n=343	n=230	n=275	n=159
Women (n=2395)	ref.	1.06 (0.90, 1.26)	**1.20 (1.01, 1.42)**	1.09 (0.89, 1.33)
Number of Deaths	n=322	n=155	n=192	n=86
Men (n=1524)	ref.	1.04 (0.85, 1.26)	**1.40 (1.17, 1.69)**	0.99 (0.78, 1.27)
Race				
Number of Deaths	n=240	n=129	n=144	n=81
African American (n=1295)	ref.	1.04 (0.84, 1.30)	1.17 (0.95, 1.45)	0.84 (0.65, 1.10)
Number of Deaths	n=425	n=256	n=323	n=164
Caucasian (n=2624)	ref.	1.06 (0.91, 1.24)	**1.34 (1.15, 1.57)**	**1.21 (1.00, 1.46)**
Age				
Number of Deaths	n=273	n=103	n=219	n=75
< 65 at baseline (n=2439)	ref.	1.08 (0.86, 1.36)	**1.43 (1.19, 1.72)**	**1.39 (1.07, 1.81)**
Number of Deaths	n=392	n=282	n=248	n=170
≥ 65 at baseline (n=1480)	ref.	1.02 (0.88, 1.19)	1.17 (0.99, 1.39)	0.94 (0.77, 1.13)
Obesity				
Number of Deaths	n=443	n=262	n=274	n=132
BMI < 30 (n=2354)	ref.	1.05 (0.90, 1.23)	**1.32 (1.13, 1.55)**	0.98 (0.80, 1.21)
Number of Deaths	n=222	n=123	n=193	n=113
BMI ≥ 30 (n=1565)	ref.	1.06 (0.85, 1.32)	**1.22 (1.00, 1.50)**	1.17 (0.92, 1.48)

[a]Adjusted for enrollment wave, age, sex, race, education, hip injury, non-steroidal anti-inflammatory drugs, smoking, alcohol use, physical activity, disability, any of 6 comorbidities, BMI, low back pain

[b]Data used are multiply imputed (n=10) to estimate missing baseline values for covariates. Stratified over five birth decade cohorts, using age as the time scale, and baseline age for left truncation.

rOA=radiographic osteoarthritis