Osteoarthritis and Cartilage

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The impact of painful knee osteoarthritis on mortality: a community-based cohort study with over 24 years of follow-up

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SUMMARY

Objective: To investigate the impact of knee osteoarthritis (OA) and/or knee pain on excess mortality.
Method: We analyzed data from 4,182 participants in a community-based prospective cohort study of African American and Caucasian men and women aged ≥45 years. Participants completed knee radiographs and questionnaires at baseline and at up to three follow-ups to determine knee OA (rOA), knee pain and covariate status. Mortality was determined through 2015. We used Cox proportional hazards regression with time-varying covariates (TVC) to estimate hazard ratios (HR) and 95% confidence intervals (CI). Additional analyses stratified by sex, race and age were carried out.
Results: Median follow-up time was 14.6 years during which 1822 deaths occurred. Baseline knee radiographic osteoarthritis (rOA) was 27.7%, 38.8% at first follow-up, 52.6% at second follow-up and 61.9% at the third follow-up. Knee rOA with pain and knee pain alone were both associated with a >15% increase in premature all-cause mortality. In analyses stratified by sex, race and age, associations between knee pain, with or without knee rOA, and all-cause death were found among women, Caucasians, those ≤65 years of age, and those with a body mass index (BMI)≥30, with observed increased risks of death between 21% and 65%. We observed similar, somewhat attenuated, results for cardiovascular disease (CVD) deaths.
Conclusion: In models taking into account variables that change over time, individuals who had knee pain, alone or with knee rOA, had increased mortality. These effects were particularly strong among those obese. Effective interventions to reduce knee pain, particularly those including weight management and prevention of comorbidities, could reduce mortality.

Introduction

Osteoarthritis (OA) is a well-described chronic joint disorder with clinical manifestations including substantial synovial joint pain, swelling and stiffness. It is the most common form of arthritis affecting nearly 31 million US adults[1], with 13.7 million of those having symptomatic knee osteoarthritis[2]. The risk of developing knee OA by age 60 is 13.8%[3] which increases to 44.7% by age 85[4]. This already considerable burden of OA is projected to continue to rise reflecting the aging population and an increase in OA risk factors such as obesity[5].

Individuals with knee OA also experience increased rates of obesity and comorbidity, which can be as high as 85% in certain populations[6,7]. The links between OA and comorbidities are likely complex with evidence pointing to shared risk factors with common etiologic pathways including cardiovascular disease (CVD), type-two diabetes, and hypertension[8−10]. Further, OA can lead to significant functional limitations and depression which can lead to premature death[11].

In recent years a number of studies have investigated the association between OA and premature mortality. A 2008 review suggested modest associations of OA with all-cause mortality but noted that technical shortcomings limited their conclusions, including differing study populations, small sample size and lack of inclusion of important covariates from some of the studies[12]. A more recent meta-analysis of nine studies reported no significant association between radiographic osteoarthritis (rOA) or symptomatic OA (SxOA) with mortality, however this study also did not differentiate between joint sites affected by OA, combining estimates for hand, knee, hip and spine OA[13]. Prospective studies addressing knee OA specifically as a risk factor for premature mortality have been equivocal with some reporting lower mortality among those with knee OA[14−16] and others reporting higher mortality rates[17−19]. The conflicting results reported by these studies may be a result of limitations including measurement of knee OA at a single baseline time point, lack of inclusion of important covariates, short duration of follow up, and/or small sample sizes.

Because of the inconsistent results to date, we sought to examine associations between knee rOA and/or knee pain and all-cause as well as CVD-specific death, independent of comorbidities, in a large community-based prospective cohort with nearly 25 years of follow-up and up to four repeated measurements of knee OA and covariates.

Methods

Study design and participants

The Johnston County Osteoarthritis Project (JoCoOA) is a community-based prospective cohort study of OA in North Carolina (NC). Details of JoCoOA have been previously described[20,21]. Briefly, we recruited African Americans (AA) and Caucasians from six townships in a rural NC county. Participants were English-speaking, noninstitutionalized civilians 45 years of age or older. We enrolled participants enrolled in two waves: the first from 1991 to 1997 and additional participants were enrolled from 2003 to 2004 (Appendix Fig. I). All participants completed informed consent forms. Interviewer-administered questionnaires, clinical examinations, and radiographs were completed for all participants at baseline and at up to three follow-up time points, the last of which was completed in 2015. Our analyses included individuals with at least one evaluable knee radiograph. The Institutional Review Boards at the University of North Carolina, Chapel Hill and the Centers for Disease Control and Prevention (CDC) in Atlanta, GA have continuously approved JoCoOA.

Knee pain and rOA definitions

Knee radiographs taken at baseline and available follow-up assessments were read paired for individual participants and were blinded to clinical status and participant identification. Interpretation was completed by a single radiologist (JBR) with high weighted inter-rater (kappa = 0.86) and intra-rater reliability (kappa = 0.89)[22]. rOA was scored on the Kellgren−Lawrence (KL) scale from 0 to 4[23]. A KL grade ≥2 was indicative of having knee rOA, with a comparison to those without knee rOA (i.e., KL grade <2). A KL grade ≥3 was indicative of having _severe_ knee rOA, with a comparison to those without severe knee rOA (i.e., KL grade <3). Total knee replacement indicated in questionnaire data as being necessary because of OA was also classified as having knee rOA.

For knee pain assessments at baseline and all available follow-up time points, participants were asked about knee pain through the following question, "On most days, do you have pain, aching or stiffness in your [right/left] knee?" Participants with SxOA are a subset of individuals with knee rOA who responded yes to pain in the same knee that was classified rOA, with a comparison to those without knee SxOA (i.e., KL grade <2 and/or no knee pain, but can have one without the other).

We created a separate 4-level combined knee rOA/pain variable with mutually exclusive and exhaustive groupings to assess the independent effects of rOA status (rOA and knee pain) at each time point according to an individual's worst knee on later risk of death. These subgroups included: neither knee rOA nor knee pain in either knee (referent); knee rOA but no pain in the same joint; knee pain but no knee rOA in either joint; and both rOA and pain in the same knee (SxOA). Since our analysis was carried out on a person-level, there were some participants who had discordant joint knee rOA and pain (i.e., pain without rOA in one knee and rOA but no pain in the other knee) (Appendix Table I). We chose a conservative approach and included those participants in the knee rOA alone (without pain) group. A sensitivity analyses placing those participants instead in the knee pain alone group was conducted (Appendix Table II, Model 2).

To capture more precisely how knee rOA and/or pain affects mortality over 25 years, we were able to measure our knee rOA and pain predictors as they changed over time. Knee pain could alternate values from one time point to the next (i.e., have knee pain at one assessment but then have no knee pain at the next assessment). Knee rOA status could change at most once (i.e., from having no knee rOA at one assessment to having knee rOA at the next assessment); once a participant developed rOA, it could not be reversed.

Covariates

Covariate definitions and categories are summarized in Appendix Table III. Covariates which did not change over time, or changed at the same rate for all participants (i.e., age) included: enrollment wave (first or second), age (continuous), birth cohort (by decade), sex (male or female), race (AA or Caucasian), and self-reported formal education level (<12 yrs or ≥12 years). Covariates that could change over time but once developed could not be reversed included: hip rOA (KL grade ≥2), and self-reports of the following: knee injury (ever or never), smoking status (ever smoker or never smoker), alcohol use (ever user or never user) and self-reported comorbidities (yes or no) including cancer, liver disease, hypertension, diabetes or CVD. CVD was defined as reporting heart attack or other heart problems, stroke, circulation problems and/or use of CVD-specific medications. Also considered in models were time-varying covariates (TVC) which could alternate over time including body mass index (BMI) and self-reports of the following:

use of non-steroidal anti-inflammatory drugs (NSAIDS) (yes or no), meeting the CDC guidelines for moderate/vigorous physical activity (MVPA) (yes or no) and depressive symptoms. Depressive symptoms (depression) at the T0, T1 and T2 time points were defined as having a Center for Epidemiologic Studies Depression (CES-D) score of ≥16; at the T3 time point depression was defined as having a Patient Reported Outcomes Measurement Information System Depression (PROMIS-D) score of ≥18[24].

Mortality

Vital status was determined for all participants at each follow-up assessment. Follow-up assessments took place from 1999 to 2004 (T1), 2006–2010 (T2) and 2013–2015 (T3). After the T3 follow-up was completed, individuals not known to be alive (died, moved out of the area or lost to follow-up) were submitted to the National Death Index (NDI) to ascertain date and cause of death through December 31, 2015. Additionally, known deaths not found through NDI records but confirmed through local vital records searches were also used. 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

Descriptive statistics for covariates at baseline and at follow-up time points were computed. Continuous variables are presented as means and standard deviations (±SD) and categorical variables are presented as frequencies and percentages. All tests were two-sided and considered statistically significant at the 0.05 level. All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC).

Covariate information for at least one baseline measure was missing for 8.2% of the participants (Fig. 1). We used a multiple imputation (MI) model that included all baseline variables to impute missing baseline covariate values (all binary). Logistic regression was used to impute binary baseline covariates by fully conditional specification methods (FCS) which performs best for missing-at-random (MAR) patterns and a missing proportion of less than 50%[25]. Twenty imputed datasets were generated so that the number of imputations were at least equal to the percent of data missing one or more covariates[26] (for more information see the Appendix). We used a last observation carried forward approach for binary missing data at subsequent follow-up assessments, where missing data ranged from 0.1 to 0.3% (Appendix Table IV). Further, a complete-case sensitivity analysis was carried out (Appendix Table II, Model 3).

Kaplan–Meier methods[27] were used to generate survival curves by baseline knee rOA and knee pain status, unadjusted and adjusted for baseline age and sex using inverse probability weights[28]. Cox proportional hazards regression[27] with TVC changing with irregular intervals starting at baseline and at up to three follow-up assessments was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for all-cause and CVD-specific mortality in relation to knee rOA and knee pain measured over time. 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[27] and no evidence of violation of this assumption was found. While the subdistribution hazard approach is an arguably superior method to assess CVD-specific mortality[29], these methods do not yet satisfactorily handle TVC[30,31]. Therefore, in order to use our covariates which change over time, CVD-specific mortality analyses were modeled using the CVD-cause-specific hazard,

treating non-CVD mortality competing events as censored observations. Separate analyses were carried out in each of the 20 imputed datasets, then estimated parameters from all imputed datasets were synthesized to generate a single estimate according to Rubin's rules[32]. All models were stratified by decade birth cohort to account for calendar effects, which is recommended when following healthy people and when the calendar effect is likely to impact the outcome, mortality, as well as other risk factors[33]. Follow-up time was calculated from 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).

Tests of interaction were performed and stratified analyses were conducted to describe associations between knee rOA status (rOA and/or knee pain) measures and all-cause or CVD-specific survival by each of obesity (BMI<30 and BMI≥30), age group split at the median (<65 yrs and ≥65 yrs), race (Caucasian and AA) and sex (male and female).

Sensitivity analyses: We carried out two additional sensitivity analyses. One excluded deaths occurring in the first year of follow-up after baseline and the second used only knee rOA measures from the baseline time point to assess whether study attrition may have affected our results (Appendix Table II, Models 4 & 5, respectively).

Results

The characteristics of JoCoOA cohort by study visit are reported in Table I. Mean age at baseline was 61.0 years, 63.2% were women, 34.3% AA and 75.0% were from the original study enrollment. There were 27.7% participants in our population with knee rOA at baseline, which increased to 38.8% at first follow-up, 52.6% at second follow-up and 61.9% by the third follow-up. Individuals with only a baseline assessment had higher frequencies of both knee rOA and knee pain (35.5% and 49.0%, respectively; data not shown). Similar to knee rOA, the percentage of obese individuals and those with diabetes increased over time. Through 2015, median follow-up time was 14.6 years and there were 1,822 deaths overall, 677 (37.2%) of which resulted from CVD.

In models taking into consideration that covariates may change over time, we did not observe any increase in hazard for knee rOA when compared to those without rOA with respect to either all-cause or CVD-specific mortality (Table II). We observed a similar lack of association for individuals with severe knee rOA. However, we observed a 13% increased hazards for all-cause mortality among those with knee rOA who also had pain in the same joint (SxOA) when compared to those without SxOA (HR = 1.13, 95% CI = 1.01–1.26). Comparable associations with knee SxOA were observed for CVD-specific death, and tended to be somewhat stronger and which remained statistically significant after full covariate adjustment (including obesity, diabetes, and CVD) (HR = 1.19, 95% CI = 1.00–1.43).

We present unadjusted and adjusted Kaplan–Meier survival curves for all-cause mortality according to the 4-level combined knee rOA/pain variable at baseline. Unadjusted survival estimates (Fig. 2(a)) indicate that those with knee SxOA had the worst survival, wherein we observed 50% survival at 15.3 years; median survival was 17.1 years among those with knee rOA alone and 20.2 years for those with knee pain alone. When taking age and sex into account, however, median survival times for those with SxOA (18.3 years) and knee rOA (21.6 years) increased, while median survival decreased for those with neither knee rOA nor knee pain (22.9 years) and for those with knee pain alone (19.0 years) (Fig. 2(b)).

Results from Cox proportional hazards models to estimate risk of death for time-varying values of the 4-level combined knee rOA/ pain variable are presented in Table III. In covariate-adjusted
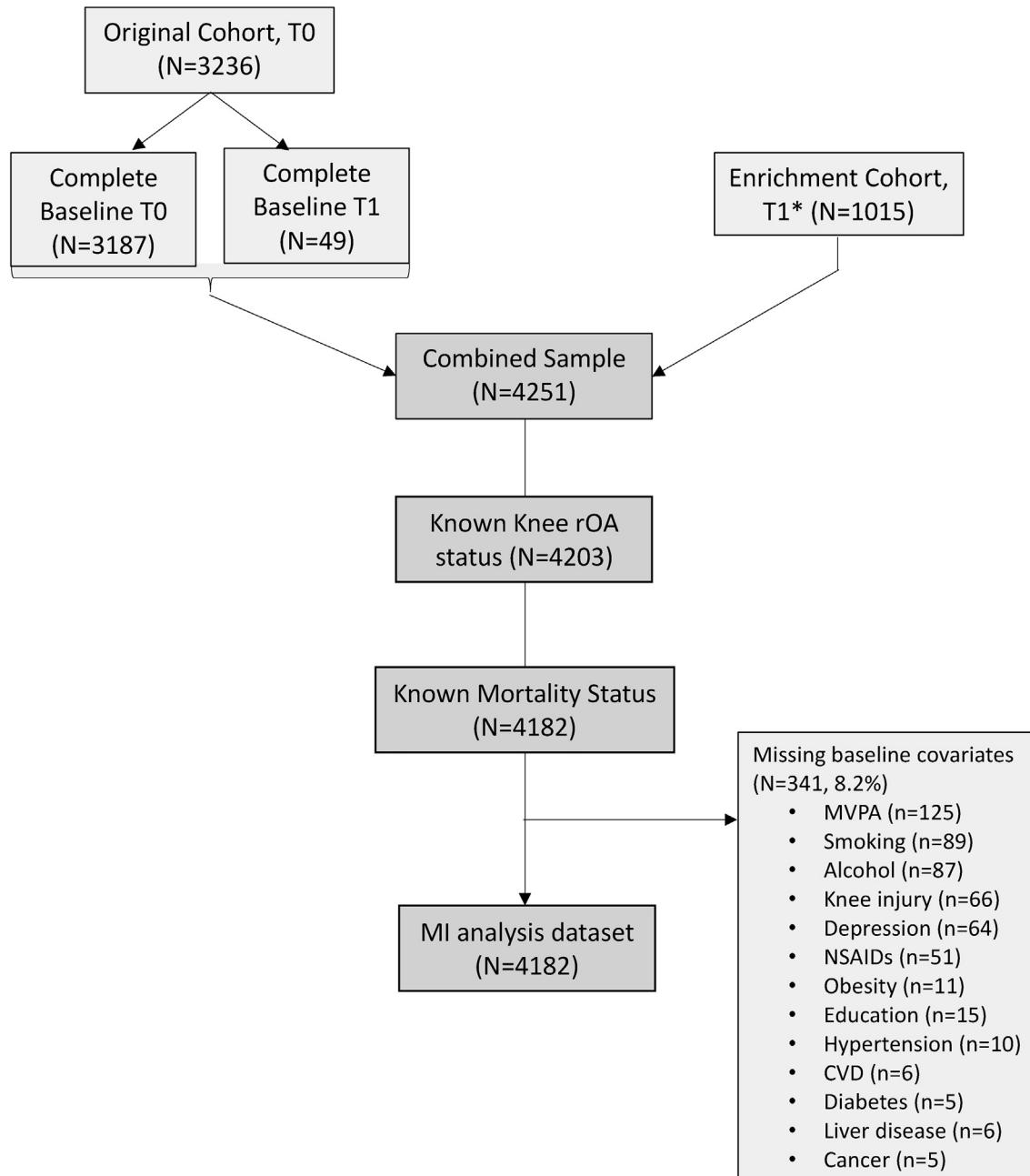
Fig. 1. Johnston County Osteoarthritis Study − Baseline Knee rOA participants.

models, compared to those with neither knee rOA nor knee pain, we observed an increased risk of all-cause mortality in participants with knee pain alone (HR = 1.19, 95% CI = 1.04−1.35) as well as participants who have knee SxOA (HR = 1.17, 95% CI = 1.03−1.34). Similarly, we observed increased hazards for CVD-specific mortality among those having both knee rOA and pain in the same knee, although the data indicated a lack of statistical significance after adjustment for covariates. Knee rOA without pain was not associated with an increase in either all-cause or CVD-specific mortality. Results from additional models that also included hip rOA as a covariate did not differ substantially (data not shown).

Results were not substantially different from analyses which placed discordant joint knee rOA and pain in the knee pain group instead of the knee rOA group, for analyses carried out on a complete-case dataset, analyses which excluded deaths occurring

in the first year of follow-up after baseline, nor did results differ when assessing knee rOA and covariates measured only at baseline instead of TVC (Appendix Table II Models 2, 3, 4 & 5, respectively).

Stratified analyses

We examined the association between the 4-level combined knee rOA/pain variable and mortality stratified by obesity and demographics (Fig. 3). Covariate-adjusted HR estimates for all-cause mortality were increased 21−65% for knee pain with or without rOA among women, Caucasians, those under the age of 65 and those with a BMI≥30. For example, among those with a BMI≥30 we observed an increase in hazards for both knee pain alone (HR = 1.66, 95% CI = 1.31−2.10) and knee SxOA (HR = 1.47, 95% CI = 1.18−1.83), while we observed no association among those

Table I
Baseline demographic characteristics, JoCoOA Study

	Baseline ($n = 4182$) n (%) or mean (SD; range)
Demographics	
Enrollment wave	
T0 (1991−1997)	3136 (75.0)
T1ˆ (2003−2004)	1046 (25.0)
Baseline to follow-up (years)	14.7 (6.1; 0−24.6)
Age at visit (years)	61.0 (10.6; 45.0−93.6)
Female	2644 (63.2)
African American	1436 (34.3)
<High School Education	1500 (35.9)
BMI group	
<25	987 (23.6)
≥25.0 − <30	1516 (36.3)
≥30.0	1668 (39.9)
Smoker	2063 (49.3)
Alcohol use	1986 (47.5)
<150 MVPA mins/week	3444 (82.4)
NSAID use	1439 (34.4)
Comorbidities	
Cancer	50 (1.2)
Cardiovascular disease	916 (21.9)
Hypertension	1614 (38.6)
Diabetes	551 (13.2)
Depression	538 (12.9)
Liver disease	68 (1.6)
Hip rOA	1169 (28.0)
Knee rOA/pain variables	
No Knee rOA & No Knee Pain	1896 (45.3)
Knee rOA Alone (No Knee Pain)	434 (10.4)
Knee Pain Alone (No Knee rOA)	1129 (27.0)
Knee rOA & Knee Pain (SxOA)	723 (17.3)

FU=Follow-up.

with a BMI<30 (interaction *P*-value<0.01). No other statistical interaction was observed. Similar results for risk of CVD-specific death among those having knee SxOA were observed.

Discussion

In this longitudinal community-based cohort of AA and Caucasian men and women we found that individuals with knee pain or painful knee rOA have an increased risk of death from all-causes. In stratified analyses, these associations were observed among those with a BMI≥30, and among those <65 years of age at baseline. We found no association, however, between radiographic knee OA alone (without pain) and risk of death due to either all-causes or CVD specifically.

Our results follow a similar pattern as those reported in a recent study, though our estimates were not of the same magnitude[17]. Kluzek *et al.* also reported no association with rOA without pain, but about a 50% increased risk of mortality with pain only and 97% increase with both. When we looked at categories of knee rOA and knee pain separately we found that our associations were limited to those with knee pain, though there were few individuals in our study with knee rOA who did not also have pain. The study by Kluzek *et al.* was limited to women who have more reported knee pain, whereas our study includes men and older individuals who have higher mortality rates, both of which may account for the smaller estimates.

Other studies have provided inconsistent reports of increased[18], decreased[14] and no[15,16] risk of death with knee OA. Most of these studies did not distinguish between those with knee rOA and those with knee SxOA. Further, several studies used knee OA data extracted from medical records[14–16]. These individuals would be more likely to be characterized as having knee SxOA rather than knee rOA alone since they were diagnosed with knee OA by a physician only after seeking medical care, presumably due to the presence of knee pain. One other study reported a nearly two-fold increased risk of death for both SxOA as well as rOA, although in this study knee SxOA was merely a subset of those with knee rOA, and did not distinguish between knee rOA alone and knee pain alone[18]. The conflicting results from these studies may reflect the differences in data sources and definitions of knee OA.

Knee pain is not a perfect marker of radiographic knee OA[34], nor is radiographic knee OA a perfect marker for pain and disability[35]. There are other conditions which may lead to knee pain, including acute and overuse injuries, referred nerve pain and mechanical problems. Further, the definitions of knee rOA and knee pain used may affect the association between them. Our combined measure of knee rOA and knee pain allows us to assess the independent effects of both radiographic knee OA and pain on mortality. In addition, we adjusted for conditions that may affect knee pain, such as comorbidities and knee injury. Further, the impact of pain on mortality was found in a group of individuals who are at high risk of having other morbidity including CVD, cancer and diabetes which were accounted for in the analyses. Our results suggest that it is the symptoms of knee rOA, rather than the structural damage, that is associated with excess mortality.

While there is a large and growing body of literature on pain and mortality, the published results in general are restricted to non-site-specific chronic or widespread pain[36]. A possible explanation for the increase in mortality is that OA leads to a cycle of low

Table II
Hazard ratios for the association between knee rOA at up to 3 follow-up assessments and all-cause and CVD casue-specific mortality, JoCoOA Study*

Cohort	No knee rOA	Knee rOA HR (95% CI)	No knee SxOA	Knee SxOA HR (95% CI)	No Severe knee rOA	Severe knee rOA HR (95% CI)
	$N = 2308$	$N = 1874$	$N = 3005$	$N = 1177$	$N = 3181$	$N = 1001$
All-cause mortality						
Number of deaths	$n = 977$	$n = 845$	$n = 1272$	$n = 550$	$n = 1392$	$n = 430$
Model 1†	ref.	1.02 (0.92, 1.12)	ref.	**1.15 (1.03, 1.27)**	ref.	0.98 (0.88, 1.10)
Model 2‡	ref.	1.01 (0.92, 1.11)	ref.	**1.15 (1.03, 1.28)**	ref.	0.99 (0.88, 1.11)
Model 3§	ref.	0.99 (0.90, 1.09)	ref.	**1.13 (1.01, 1.26)**	ref.	0.96 (0.86, 1.08)
CVD, specific mortality						
Number of deaths	$n = 352$	$n = 325$	$n = 455$	$n = 222$	$n = 505$	$n = 172$
Model 1†	ref.	1.05 (0.89, 1.22)	ref.	**1.26 (1.07, 1.49)**	ref.	1.06 (0.88, 1.26)
Model 2‡	ref.	1.04 (0.89, 1.22)	ref.	**1.27 (1.07, 1.50)**	ref.	1.08 (0.90, 1.29)
Model 3§	ref.	0.99 (0.84, 1.16)	ref.	**1.19 (1.00, 1.43)**	ref.	1.01 (0.84, 1.22)

Bold indicates two-sided *p*<0.05.
rOA=radiographic osteoarthritis; SxOA=symptomatic rOA

* Data used are multiply imputed to estimate missing baseline values and apply the last observation carried forward for covariates missing at follow-up assessments.

† Adjusted for enrollment wave, age, sex, race, education.

‡ Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity.

§ Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, obesity, diabetes, cardiovascular disease.
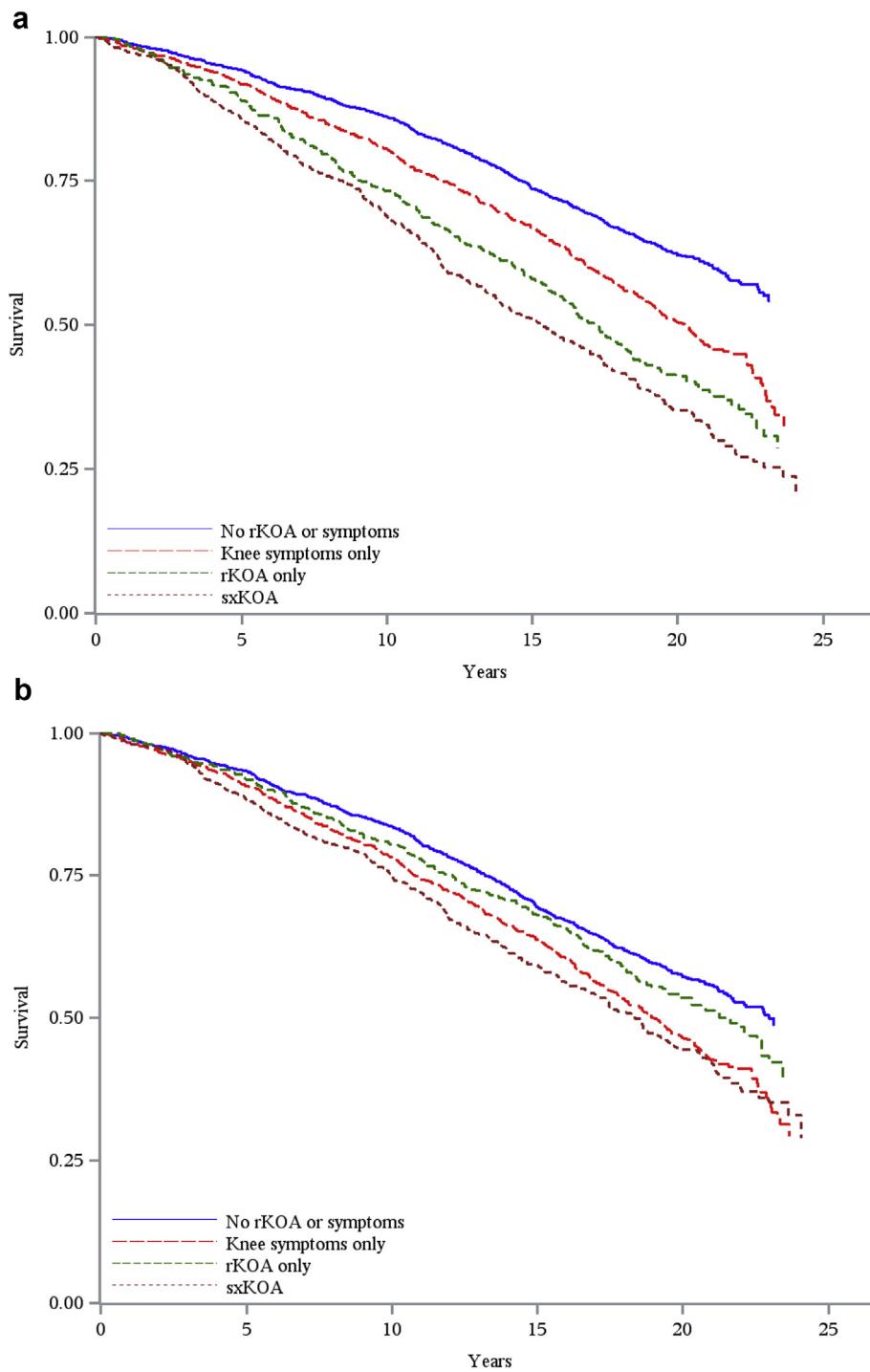
Fig. 2. Kaplan–Meier survival curves for mortality by baseline knee rOA and/or knee pain group, unadjusted (a) and adjusted for age and sex (b).

physical activity, pain, disability, increased BMI and serious comorbidities such as diabetes and CVD[37,38]. Pain resulting from OA is a leading cause of disability, and its impact on mortality is supported by reports that OA accounts for a large portion of the years lived with disability and quality-adjusted life-years lost[39,40]. OA has also been shown to share many risk factors with CVD including age, obesity, hypertension and NSAID use, and it has been suggested that these conditions have overlapping causal pathways[41]. The

inflammatory processes in certain comorbidities including CVD are known to be associated with increased risk of premature death, and recent reports suggest that those with OA may experience a low-grade chronic inflammation similar to CVD[42]. Further, symptom-atic knee OA itself has been shown to increase risk of CVD[43], although our results for CVD-specific mortality did not differ appreciably from those seen for all-cause mortality. While we were able to include many of these comorbid conditions in our models,

Table III
Hazard ratios for the association between knee rOA and knee pain at up to 3 follow-up assessments and all-cause and CVD cause-specific mortality, JoCoOA Study*

| Cohort	Neither knee rOA nor pain	Knee rOA without pain HR (95% CI)	Knee pain without rOA HR (95% CI)	Both knee rOA and pain HR (95% CI)
	N = 1271	N = 561	N = 1173	N = 1177
All-cause mortality				
Number of deaths	n = 511	n = 264	n = 497	n = 550
Model 1†	ref.	0.98 (0.85, 1.13)	**1.23 (1.09, 1.40)**	**1.21 (1.07, 1.37)**
Model 2‡	ref.	0.97 (0.84, 1.12)	**1.22 (1.07, 1.39)**	**1.21 (1.06, 1.37)**
Model 3§	ref.	0.95 (0.83, 1.09)	**1.18 (1.03, 1.34)**	**1.17 (1.02, 1.33)**
CVD-specific mortality				
Number of deaths	n = 189	n = 88	n = 178	n = 222
Model 1†	ref.	0.90 (0.71, 1.14)	1.22 (0.99, 1.51)	**1.32 (1.08, 1.61)**
Model 2‡	ref.	0.90 (0.71, 1.14)	**1.24 (1.00, 1.54)**	**1.33 (1.08, 1.64)**
Model 3§	ref.	0.87 (0.68, 1.10)	1.16 (0.93, 1.44)	1.21 (0.98, 1.50)

rOA=radiographic osteoarthritis
* Data used are multiply imputed to estimate missing baseline values and apply the last observation carried forward for covariates missing at follow-up assessments.
† Adjusted for enrollment wave, age, sex, race, education.
‡ Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity.
§ Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, obesity, diabetes, cardiovascular disease.
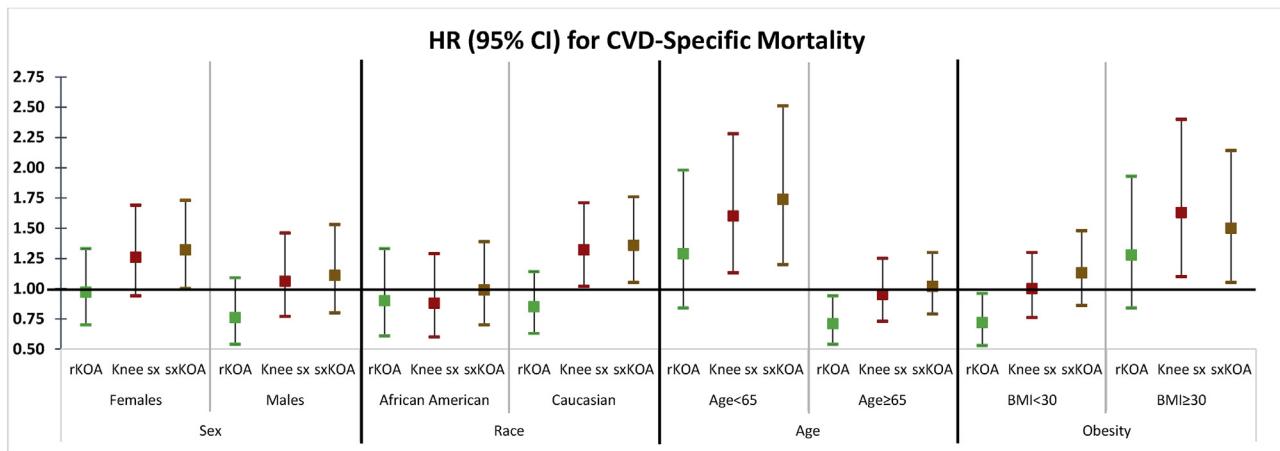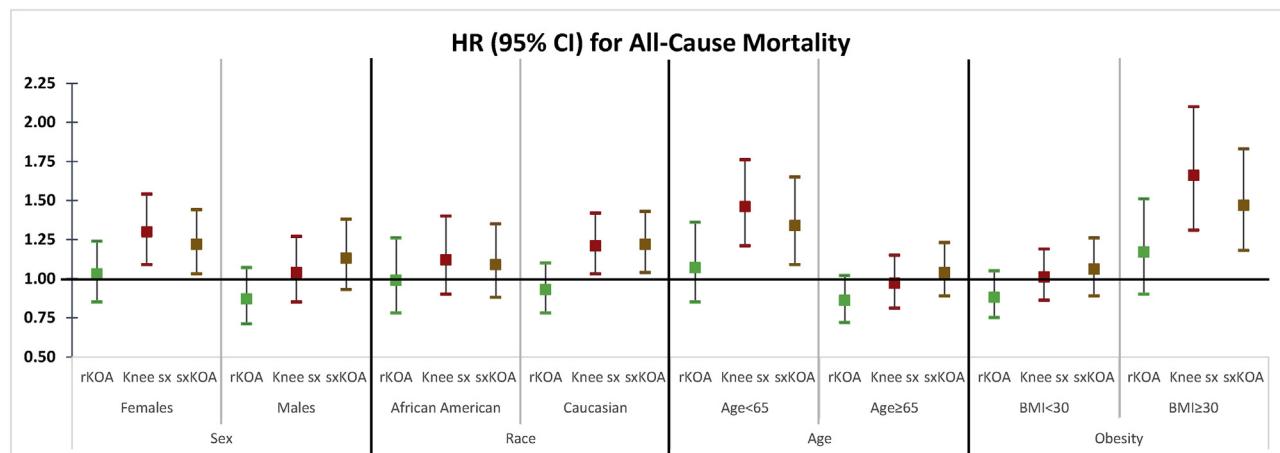
Fig. 3. Adjusted[a] hazard ratios (HR) and 95% confidence intervals (CI) for the association between knee rOA and knee pain on all-cause mortality stratified by demographics and obesity, JoCoOA Study. [a]Adjusted for enrollment wave, age, sex, race, education, knee injury, cancer, non-steroidal anti-inflammatory drugs, hypertension, smoking, liver disease, alcohol use, depression, physical activity, obesity, diabetes, cardiovascular disease.

we believe there is some aspect of knee pain that is not explained by other mortality-associated conditions accounted for in our study that warrants further study.

Obesity is known to have many deleterious effects on an individual's health. In addition to increased risk of other comorbidities and disability, increasing BMI has been shown to be linearly associated with more pain, where those who are obese have been shown to have 68% more pain than those who are not obese[44]. Further, those with a BMI>30 have also been shown to have greater risk of death than those with a BMI 18.5–25[45]. Our

results are consistent with these reports; we found that among participants with a BMI≥30, individuals who also had knee pain and/or knee rOA had the greatest risks of both all-cause and CVD-specific mortality.

When we examined associations according to demographics, results suggested greater mortality for those with knee pain with or without knee rOA among women, Caucasians and those under the age of 65. Our results are similar to those of a study among women aged 45–64 years of age in which those with knee pain or knee SxOA were at increased risk of death[17]. There are several plausible explanations for these observed results. Previous studies have shown that women with knee SxOA have higher rates of low function[46] and depression[47], both of which are associated with higher mortality rates[48,49]. Further, women in our study tended to have higher BMI than men. Our finding of greater mortality with knee pain/rOA among those who were younger may suggest a role for long-term psychological distress and disability. For example, it is possible that those who are younger may develop disability early on, leading to depression, reduced physical activity and increasing BMI resulting in the development of comorbidities at a younger age than expected.

Our study has several advantages. In contrast to previous studies that have measured knee OA at baseline and assessed its association with mortality thereafter, we utilized the richness of our dataset that included a baseline knee rOA/pain measurement and covariates with up to three follow-up assessments, yielding nearly 25 years follow-up. By using our longitudinal data we were able to study the effect of knee rOA/pain as it changes over time on mortality while also accounting for changing comorbidities, representing an improvement over traditional studies based on survival analyses relating all future survival to a risk factor and covariates assessed at a single moment in time[14,15,17]. Further strengths include that JoCoOA is a community-based longitudinal study with nearly 25 years of follow up that includes both men and AA, two sub-populations that have not been widely studied. Our assessment of mortality included the use of both NDI records as well as county vital records to determine whether a death occurred. Knee OA in our study was radiographically confirmed and read by a single radiologist, includes severity of disease and was measured at several different time points to account for possible change in rOA status over time. Furthermore, we adjusted our analyses for several well-known mortality-associated factors which are common in knee OA patients that warranted special attention in our study, including comorbidities and NSAID use. However, the possibility of residual confounding by unrecognized factors cannot be excluded. Finally, in order to assess the possibility of early deaths resulting from other causes, additional analyses excluding deaths in the first year of follow-up did not yield different results.

Limitations include that our measure of pain was somewhat crude in that it was defined as having at least mild knee pain most days. We also do not have a consistent measure of disability across follow-up assessments. Also, we do not have a precise date of rOA occurrence as it was measured at baseline, then at the three follow-up time periods of the study which varied in length. However, we used a Cox proportional hazards regression approach using a counting process which assumes the individual is continuously at risk of the event until the end of the follow-up period[27]. Our study has a long follow-up and as such is subject to incurring deaths due to natural causes and normal ageing. However, in our survival curves we see a clear separation of increasing deaths over time for those with knee rOA and/or knee pain even at longer observation times compared with those who have neither. Further, survival analyses take into account the timing of death and our results suggest that those with knee rOA and/or knee pain tend die sooner than those who do not. We also experienced some study attrition

over time. Our sensitivity analyses using baseline measures only as predictors of later mortality were similar to those using TVC. Since using baseline only information likely misses developing OA cases, we are likely underestimating the effect so we feel ours is a conservative approach.

Our results demonstrate an increased risk of mortality for individuals who had knee pain, alone or with knee rOA. These effects were particularly strong for those who were obese. Interventions should be targeted toward reducing pain, weight loss/maintenance and avoiding future comorbidities. Future studies should focus on defining pain phenotypes in knee rOA to identify subsets of individuals who are more likely to die in order to create more targeted interventions aimed at reducing pain and disability which have been linked to increased mortality.

Author contributions

1) Conception and design: RJC, TAS, JMJ, LFC. Acquisition of data: RJC, JBR, JMJ, LFC. Analysis and interpretation of data: RJC, CA, TAS, EL, LFC.
2) Drafting the manuscript: RJC, CA, LFC. Critical revisions for important intellectual content: All authors.
3) Final approval of the version to be submitted: All authors.

Competing interests

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2018.12.008.

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