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Title: Knee osteoarthritis, potential mediators, and risk of all-cause mortality: data from the Osteoarthritis Initiative

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ABSTRACT

Objective

To assess the relation of symptomatic knee osteoarthritis (OA), knee pain, and radiographic knee OA to all-cause mortality and identify mediators in the causal pathway.

Methods

Participants from the Osteoarthritis Initiative were divided into four groups: (1) symptomatic knee OA (i.e., both radiographic knee OA [Kellgren and Lawrence grade ≥2] and knee pain); (2) knee pain only; (3) radiographic knee OA only; and (4) neither radiographic knee OA nor knee pain. We examined the relation of knee OA status to all-cause mortality using a multivariable Cox-proportional model and assessed the extent to which the association was mediated by disability, physical (PCS) and mental component summary scores (MCS) of quality of life (QoL), and oral pain-relief medications (i.e. nonsteroidal anti-inflammatory drugs and opioids) use.

Results

Among 4,796 participants, 282 died over the 96-month follow-up period. Compared with those with neither radiographic knee OA nor knee pain, multivariable-adjusted hazard ratios (HRs) of mortality were 2.2 (95% confidence interval [CI]: 1.6-3.1) for symptomatic knee OA, 0.9 (95%CI: 0.6-1.4) for knee pain only, and 2.0 (95%CI: 1.4-2.9) for radiographic knee OA only, respectively. Indirect effects (HRs) of symptomatic knee OA on mortality via disability and PCS of QoL were 1.1 (95%CI: 1.0-1.4) and 1.2 (95%CI: 1.0-1.4), respectively. No apparent mediation effect was observed through either MCS of QoL or oral pain-relief medications use.

Conclusion

Participants with either symptomatic or radiographic knee OA were at an increased risk of all-cause mortality. Increased risk of mortality from symptomatic knee OA was partially mediated through its effect on disability and PCS of QoL.

SIGNIFICANCE AND INNOVATIONS

- Both symptomatic knee OA and radiographic knee OA were associated with an increased risk of all-cause mortality. These findings underscore the importance of developing appropriate preventive and treatment strategies to reduce the risk of knee OA.

- The increased risk of all-cause mortality from symptomatic knee OA was mediated through disability and PCS of QoL, suggesting that more efforts should focus on improving function and QoL to reduce all-cause mortality among patients with symptomatic knee OA.

Osteoarthritis (OA) is the most common joint disorder (1, 2), affecting approximately 10% of men and 18% of women aged 60 years or older around the world (3, 4). Besides its tremendous impact on morbidity and disability (5, 6), several studies also found that knee or hip OA were associated with an increased risk of all-cause mortality (7-14).

The mechanisms linking OA to mortality were not clearly understood. Such knowledge, however, has an important clinical implication because it would guide us to develop a more efficient intervention program that specifically targets a particular mechanism for the outcome. To our knowledge, only two studies explored the potential mechanisms linking OA to all-cause mortality (11, 12). The studies showed that an increased risk of all-cause mortality from OA was partly mediated through its effect on either walking disability (11) or physical function impairment (12), but none of them found that an increased all-cause mortality was mediated through nonsteroidal anti-inflammatory drugs (NSAIDs) use, a potential risk factor for an increased risk of either cardiovascular or gastrointestinal diseases mortality (15, 16). In both studies, however, potential mediators were either assessed at baseline or at the end of follow-up; thus, the time sequence from knee OA status to mediators to death was not clearly delineated.

To fill this knowledge gap, we examined the relation of knee OA status (i.e., symptomatic knee OA, knee pain only, radiographic knee OA only, and knee with neither radiographic OA nor pain) to the risk of all-cause mortality among participants in the Osteoarthritis Initiative (OAI). In addition, we assessed the extent to which three putative mediators, i.e., disability, quality of life (QoL), and oral pain-relief medications (i.e., NSAIDs and opioids) may impact the effect of OA on the risk of all-cause mortality.

PATIENTS AND METHODS

Study Design and Subjects

OAI is a multi-center observational study of natural history of OA and its risk factors. Individuals aged between 45 to 79 years were recruited from four clinical sites: Baltimore MD, Pittsburgh PA,

Pawtucket RI, and Columbus OH. Data from each participant were collected at baseline and at each annual follow-up visit. A detailed description regarding the rationale and approach of OAI can be found at https://nda.nih.gov/oai/about-oai.

Assessment of Knee OA and Pain

Weight-bearing semi-fixed posteroanterior knee radiographs were obtained using a standard protocol. All radiographs were read by both a musculoskeletal radiologist and a rheumatologist. If there was a disagreement as to whether the knee had radiographic OA, the reading was adjudicated by a panel of three experienced readers including the two who originally read the radiographs and another rheumatologist. A consensus reading was reached when at least two of the three readers agreed. A knee was defined as having radiographic OA if its Kellgren and Lawrence grade ≥2. Knee pain (absent/present) was based on a self-report of whether participant had pain, aching, or stiffness in their right or left knee on most days for at least one month within the past year. This definition of knee pain has been employed previously using data from OAI (17) and in combination with radiographic knee OA to define symptomatic knee OA (18).

Participants were categorized into four groups: (1) symptomatic knee OA, i.e., at least one knee having both radiographic OA and pain; (2) knee pain only, i.e., at least one knee having pain but neither knee having both pain and radiographic OA; (3) radiographic knee OA only, i.e., at least one knee having radiographic OA but neither knee having pain; or (4) knee with neither radiographic OA nor pain. We assigned a participant into one of the four categories based on the following order: symptomatic knee OA, knee pain only, radiographic knee OA only, and knee with neither radiographic OA nor pain. For example, a participant was assigned to "knee pain only" category if s/he had radiographic OA on one knee, had pain on the contralateral knee, but had no knee with both radiographic OA and pain.

Assessment of All-cause Mortality

All-cause mortality, hereafter referred to as mortality, during the 96-month follow-up period was

confirmed and adjudicated based on autopsy report, coroner's report, death certificate, National

Death Index, obituary, or Social Security Death Index (19).

Assessment of Potential Confounders

Information on age, sex, race, height, weight, education level, weekly alcohol consumption,

smoking habits, history of knee injury, comorbidities, depressive symptoms and widespread pain

were obtained at baseline. Body Mass Index (BMI) was computed as weight (kg)/ height (m^2). The

modified Charlson comorbidity index was computed based on self-reported comorbidities (20),

and the presence of depressive symptoms was classified using a score ≥16 on the Center for

Epidemiologic Studies Depression Scale (21). Widespread pain was defined as pain above and

below the waist, pain on the right and left sides of the body, and axial pain based on a standard

homunculus (22).

Assessment of Mediators

Three putative mediators were assessed at the closest follow-up visit prior to death, or prior to the

last follow-up visit if participant was lost to follow-up, or prior to the end of follow-up (i.e.,

96-month follow-up visit). These included: 1) disability, measured by the physical function

subscale (range from 0 to 68) of Western Ontario and McMaster Universities Osteoarthritis Index

(23); 2) physical and mental component summary scores of QoL (range from 0 to 100), assessed

with the 12-item Short-Form Health Survey, i.e., PCS of QoL and MCS of QoL (24, 25); and 3)

the use of oral pain-relief medications (i.e., NSAIDs and opioids) that was collected by

questionnaires in the OAI database. Participants were asked whether they had used prescription or

over-the-counter medications (acetaminophen, NSAIDs, coxibs and opioids) for joint pain or

arthritis more than half of the days of the month, in the past 30 days (26).

Statistical Analysis

Person-years of follow-up for each participant were computed as the amount of time from the date

of the baseline examination to the date of death, the last date of contact, or the end of follow up

(i.e., 96-month follow-up visit). Mortality rates for each knee OA category were calculated by dividing the number of deaths by the number of person-years of follow-up. We fitted a Cox proportional-hazards model to determine the relation of knee OA status at baseline to the risk of mortality. In the multivariable Cox proportional-hazards model, we adjusted for baseline age, sex, race, BMI, education level, weekly alcohol consumption, smoking status, history of knee injury, modified Charlson comorbidities index, depressive symptoms and widespread pain. We tested the proportional hazards assumption using the Kolmogorov supremum test.

We used a marginal structural model to assess the extent to which the association between knee OA status and mortality (i.e., total effect) was mediated through each of the putative mediators (27). Specifically, we decomposed the total effect of knee OA status on mortality into two components: 1) the indirect effect (or mediated effect), i.e., the effect of knee OA status on mortality mediated through each of the three mediators, i.e., disability, PCS/MCS of QoL and oral use of pain-relief medications; and 2) the direct effect, i.e., the effect of knee OA status on mortality that was not through a specific aforementioned mediator. In addition, we estimated the percentage of the total effect that was mediated via each mediator using the following formula: [(indirect effect - 1)*direct effect]/(indirect effect*direct effect - 1)*100% (28).

We conducted two sensitivity analyses to assess the robustness of our study findings. First, we used a new algorithm to define knee OA status at baseline according to the following order: symptomatic knee OA, radiographic knee OA only, knee pain only, and knee with neither radiographic OA nor pain. For example, a participant was assigned to "radiographic knee OA only" category if s/he had radiographic OA on one knee, had pain on the contralateral knee, but had neither knee with both radiographic OA and pain; whereas a participant was assigned to "knee pain only" category if s/he had knee pain on at least one knee but had neither knee with radiographic OA. Participants who were assigned to "symptomatic knee OA" (i.e., at least one knee having both radiographic OA and pain) or to "knee with neither radiographic OA nor pain" categories based on the previous algorithm did not change their knee OA status. Second,

considering that knee OA status of a participant may change during the follow-up period, we used the knee OA status right before the mediators were assessed. For example, if a participant with neither radiographic knee OA nor pain at baseline developed radiographic knee OA at 24-month follow-up visit, and this person did not develop knee pain since then, his/her knee OA status was assigned to "radiographic knee OA only" category, and his/her follow-up time would start from the date of 24-month follow-up visit. Data on confounders were also updated using the information collected at the closest follow-up visit prior to the assessment of knee OA status. We then took the same approach as described above to examine the relation of each of the OA status derived from these two new definitions to the risk of mortality and estimate its direct and indirect effects through each mediator.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the 4,796 participants at baseline, 6.2% (n=297) did not have adequate data for assessment of either radiographic knee OA or knee pain; thus, they were excluded from the analyses. Of the remaining, 31% (n=1,387) participants had symptomatic knee OA, 19% (n=856) had knee pain only, 25% (n=1,117) had radiographic knee OA only, and 25% (n=1,139) had neither radiographic knee OA nor knee pain. Compared with those with neither radiographic knee OA nor knee pain, participants with symptomatic knee OA were more likely to be non-white, had lower percentage of college education, higher BMI and disability score, more comorbidities, depressive symptoms, widespread pain, knee injury history, and oral pain medications use. They also had lower PCS and MCS of QoL (**Table 1**).

During the 96-month follow-up period, 282 deaths occurred (**Table 2**). Participants with symptomatic knee OA had the highest mortality rate (15.7/1,000 person-years), followed by those with radiographic knee OA only (14.1/1,000 person-years) and those with neither radiographic knee OA nor knee pain (9.4/1,000 person-years). Participants with knee pain only had the lowest

mortality (7.9/1,000 person-years). Compared with those with neither radiographic knee OA nor knee pain, the multivariable-adjusted hazards ratios (HRs) and their 95% confidence intervals (CIs) of mortality were 2.2 (95%CI: 1.6 to 3.1), 0.9 (95%CI: 0.6 to 1.4), and 2.0 (95%CI: 1.4 to 2.9) for the participants with symptomatic knee OA, knee pain only, and radiographic knee OA only, respectively.

As shown in **Table 2** and **Figure 1**, the indirect effect (HR) of symptomatic knee OA on mortality through PCS of QoL was 1.2 (95%CI: 1.0 to 1.4) and the percentage of mediation was 26.5%. The indirect effect of symptomatic knee OA on mortality via disability was borderline level of statistically significant (HR=1.1, 95%CI: 1.0 to 1.4, percentage of mediation: 22.4%). No apparent mediation effect was observed via either MCS of QoL or the use of oral pain-relief medications. An increased risk of mortality observed among participants with radiographic knee OA only was mediated through none of three aforementioned mediators.

The sensitivity analysis with the new algorithm, where the order of "radiographic knee OA only" preceded that of "knee pain only" to define a participant's knee OA status at baseline, showed that the results did not change materially (**Table 3**). When we used updated data to define knee OA status, participants with symptomatic knee OA and those with radiographic knee OA only still experienced a higher mortality than those with neither radiographic knee OA nor knee pain (**Table 4**). The multivariable-adjusted HRs were 2.0 (95% CI: 1.4 to 2.9) and 1.7 (95% CI: 1.2 to 2.4), respectively. The indirect effects of symptomatic knee OA on mortality through PCS of QoL (HR=1.2, 95%CI: 1.0 to 1.5, percentage of mediation: 38.9%) and disability (HR=1.7, 95%CI: 1.5 to 2.0, percentage of mediation: 85.5%) were greater than previous findings. However, no apparent mediation effect was observed via either MCS of QoL or the use of oral pain-relief medications. The association between radiographic knee OA only and risk of mortality was mediated by none of the three aforementioned mediators. There was no statistically significant relation of knee pain only to the risk of mortality; however, its direct and indirect effects via two mediators (i.e., disability score and PCS of QoL) showed an apparent opposite direction when a

participant's knee OA status was defined right before the mediators were assessed, indicating a potential inconsistent mediation.

DISCUSSION

Using the data collected from OAI, we found that all-cause mortality among participants with either symptomatic or radiographic knee OA only was higher than those with neither knee OA nor knee pain; however, no such an association was observed among participants with knee pain only. An increased mortality observed among participants with symptomatic knee OA was partly mediated through its effect on either disability or PCS of QoL.

To date, at least nine studies have examined the relation of knee OA to all-cause mortality (7-11, 13, 14, 29, 30). Of them, seven studies reported that knee OA was associated with an increased risk of mortality (7-11, 13, 14). Of the studies that reported a positive association between knee OA and mortality, four (7-9, 11) showed that patients with symptomatic knee OA had an increased mortality compared with those with neither radiographic knee OA nor knee pain; two studies (13, 14) found that individuals with radiographic knee OA experienced a higher risk of mortality than those without radiographic knee OA, and one study reported an excess mortality in people with either symptomatic or radiographic OA of the knee or hip compared with the general population (10). Our findings are consistent with those of previous studies, indicating that knee OA, regardless of their symptomatic status, was associated with an increased risk of all-cause mortality.

Several mechanisms linking knee and hip OA to an increased mortality have been postulated, including physical function impairment (e.g., walking disability) and pain-relief medications use (e.g., NSAIDs use). For example, results from the Wuchuan OA study showed that the relation of symptomatic knee OA to all-cause mortality was almost entirely (96.8%) mediated through its effect on walking disability (11). Similar finding was also observed in the Studies of Osteoporotic Fracture although the percentage of the total effect of hip OA through the mediation of physical

function was smaller (42.9%) (12). Our study found that 26.5% of mortality among the patients with symptomatic knee OA were mediated through the poor physical function.

Interestingly, neither Wuchuan OA study nor Studies of Osteoporotic Fracture found that NSAIDs use, a potential risk factor for cardiovascular or gastrointestinal diseases, mediated the relation of OA to the risk of mortality. The lack of statistical power was also evident in the current study, which showed that only 12.0% of mortality from symptomatic knee OA were mediated through oral pain-relief medications use (i.e., NSAIDs and opioids). Since participants recruited into OAI consisted of those who had either knee OA or were at an increased risk of knee OA (i.e., a high-risk population), NSAIDs and opioids use was common even among the participants with neither radiographic knee OA nor knee pain (21.8%), making it difficult to assess the indirect effect of symptomatic knee OA on all-cause mortality through oral pain-relief medications use. Moreover, safety profiles of individual oral pain-relief medications varied considerably, with some pain-relief medications, such as naproxen, showing no or relatively low risk of all-cause mortality compared with non-use of pain-relief medications (31, 32). Since OAI didn't specifically collect the data for each individual pain-relief medication use, we were unable to examine the mediation effect via each specific pain-relief medication. Further studies are needed to provide a more definitive examination of this association.

Although there was no apparent relation of knee pain only to the risk of all-cause mortality we observed significantly inconsistent mediation effects of knee pain only on the risk of all-cause mortality via two mediators (i.e., disability score and PCS of QoL) when we used an updated information to define a participant's knee OA status. The exact biological mechanisms for such a phenomenon are not fully understood. We postulate that the effect of knee OA status on all-cause mortality not only depends on its symptoms, such as pain, but also depends on degenerative changes in joint structure, and the latter may represent, to some extent, the degenerative process of joint structure or other organs. A few studies reported that the telomere length was shorter in chondrocytes at the osteoarthritic lesion site in the knee than those at the intact regions of cartilage

in the same joint (33-35), and telomere shortening has been linked to mortality (36-39), suggesting that structural change of radiographic knee OA might really impact mortality. In the current study we also found that participants with radiographic knee OA only experienced higher all-cause mortality than those with neither radiographic knee OA nor knee pain. This finding was consistent with other reports (13, 14) although none of the aforementioned mediators were able to explain the association.

Several characteristics of the current study are worth commenting. First, we used data from OAI, a large and well-executed population-based cohort study, to examine the association between knee OA status and risk of mortality. The exposure variable (i.e., knee OA status), potential confounders, mediators, and outcome variable (i.e., all-cause mortality) in OAI were assessed using the validated methods. Second, the selected mediators were measured at the closest visit prior to death or to the final follow-up time point, ensuring the valid time sequence from knee OA status to mediators to death. Third, when potential misclassification of knee OA status was addressed in our sensitivity analysis, the associations of symptomatic knee OA and radiographic knee OA only in relation to the mortality became stronger, and the indirect effects of symptomatic knee OA through the disability and PCS of QoL mechanisms were also greater than the findings based on the knee OA status assessed at baseline. Nevertheless, as in any observational epidemiologic studies we cannot rule out residual confounding even if a number of potential confounders have been adjusted, including Charlson comorbidities index, depressive symptoms and widespread pain. Moreover, data on the cause-specific mortality were not collected in OAI; thus, we were unable to examine the relation of knee OA status to the risk of cause-specific mortality. In addition, the detailed information on specific pain-relief medications taken by the participants was not collected as well; thus, we were unable to examine the potential medication effect via the specific pain-relief medications.

In conclusion, participants with either symptomatic or radiographic knee OA were at an increased risk of all-cause mortality. The increased risk of mortality from symptomatic knee OA was partially mediated through its effect on disability and PCS of QoL.

AUTHORS CONTRIBUTIONS STATEMENT

CZ and YZ are joint corresponding authors. CZ, YZ and YW conceived the study. YW drafted the manuscript. YZ and CZ were responsible for design of the study. NL contributed to preparation and data analysis. CZ, YZ, GL, UDTN, NEL and JW contributed to revision of the manuscript. YW, CZ and YZ were accountable for all aspects of the work. All the authors contributed to the interpretation of the data and critically reviewed the manuscript for publication. All authors read and approved the final manuscript.

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Table 1. Characteristics of Included Participants (n=4,499)

	Overall (n=4,499)	Neither Radiographic Knee OA nor Knee Pain (n=1,139)	Radiographic Knee OA Only (n=1,117)	Knee Pain Only (n=856)	Symptomatic Knee OA (n=1,387)
Age, mean (SD), years	61.2 (9.2)	60.1 (9.1)	64.0 (8.8)	58.3 (8.9)	61.5 (9.0)
Women (%)	58.1	58.1	59.4	58.4	56.8
Non-white (%)	18.8	11.4	14.6	21.6	29.8
College Graduate or Above (%)	60.3	68.3	63.3	59.4	51.8
Smoking Status (%)					
Never	79.5	79.2	80.5	79.6	78.9
Former	17.3	17.4	16.9	16.9	17.9
Current	3.2	3.5	2.6	3.6	3.2
Drinking Status (%)					
None	18.9	15.3	17.4	21.1	21.7
<1 drink/week	37.7	36.5	38.7	36.9	38.4
1-21 drinks/week	41.9	46.5	42.0	40.8	38.6
>21 drinks/week	1.6	1.8	1.9	1.2	1.3
BMI, mean (SD), kg/m²	28.6 (4.8)	26.9 (4.4)	29.0 (4.6)	27.8 (4.6)	30.2 (4.6)
Comorbidity Score, mean (SD)	0.4 (0.8)	0.3 (0.7)	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)
Depression Score, mean (SD)	6.5 (6.9)	5.4 (5.9)	5.4 (5.9)	7.3 (7.1)	7.7 (7.8)
History of Knee Injury (%)	43.4	32.3	46.0	40.2	52.0
Widespread Pain (%)	4.5	2.5	2.4	6.3	6.9
Disability Score, mean (SD)	9.5 (11.7)	4.1 (7.1)	6.5 (9.0)	10.0 (11.5)	16.0 (13.6)
PCS of QoL, mean (SD)	47.7 (9.7)	50.7 (8.4)	48.9 (8.9)	47.7 (9.8)	44.0 (10.0)
MCS of QoL, mean (SD)	53.7 (8.5)	54.1 (7.7)	54.4 (7.8)	53.1 (8.7)	53.3 (9.3)
Oral Pain Medications Use (%)	31.7	21.8	28.0	31.2	43.2

Death (%)	6.3	6.3	6.5	5.0	6.9

n, number; OA, osteoarthritis; SD, standard deviation; BMI, body mass index; PCS, physical component summary

score; MCS, mental component summary score; QoL, quality of life.

Table 2. Total, Direct, and Indirect Effect of Radiographic Knee OA Only, Knee Pain Only, and Symptomatic Knee OA on All-cause Mortality

	Neither Radiographic Knee OA nor Knee Pain (n=1,139)	Radiographic Knee OA Only (n=1,117)	Knee Pain Only (n=856)	Symptomatic Knee OA (n=1,387)
Number of Death	72	72	43	95
Deaths per 1000 Person-years (95% CI)	9.4 (7.4 to 11.8)	14.1 (11.1 to 17.8)	7.9 (5.7 to 10.6)	15.7 (12.7 to 19.2)
Total Effect, HR (95% CI)	1.0 (reference)	2.6 (1.8 to 3.6)	0.9 (0.6 to 1.3)	2.6 (1.9 to 3.6)
Total Effect, HR (95% CI) *	1.0 (reference)	2.0 (1.4 to 2.9)	0.9 (0.6 to 1.4)	2.2 (1.6 to 3.1)
Disability Score				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.1)	1.9 (1.6 to 2.3)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.1 (1.0 to 1.4)
Mediation effect (%)	-	2.0	Not same direction	22.4
PCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.1)	1.9 (1.6 to 2.2)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)
Mediation effect (%)	-	0.0	Not same direction	26.5
MCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.2)	2.2 (1.9 to 2.6)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)
Mediation effect (%)	-	0.0	Not same direction	0.0
Oral Pain Medications Use				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.1)	2.1 (1.7 to 2.5)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)
Mediation effect (%)	-	2.0	Not same direction	12.0

n, number; OA, osteoarthritis; CI, confidence interval; HR, hazard ratio; PCS, physical component summary score;

MCS, mental component summary score; QoL, quality of life.

*Adjusted for age, race, sex, body mass index, education level, weekly alcohol consumption, smoking habits, history

of knee injury, comorbidities, depressive symptoms and widespread pain.

Table 3. Sensitive Analysis (Participants with Discordant Knee Pain and Radiographic Knee OA Assigned to the Radiographic Knee OA Only Group)

	Neither Radiographic Knee OA nor Knee Pain (n=1,139)	Radiographic Knee OA Only (n=1,180)	Knee Pain Only (n=793)	Symptomatic Knee OA (n=1,387)
Number of Death	72	75	40	95
Deaths per 1000 Person-years (95% CI)	9.4 (7.4 to 11.8)	13.8 (10.9 to 17.3)	7.8 (5.6 to 10.6)	15.7 (12.7 to 19.2)
Total Effect, HR (95% CI)	1.0 (reference)	2.4 (1.7 to 3.4)	0.9 (0.6 to 1.3)	2.6 (1.9 to 3.6)
Total Effect, HR (95% CI) *	1.0 (reference)	2.0 (1.4 to 2.8)	0.9 (0.6 to 1.4)	2.2 (1.6 to 3.1)
Disability Score				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.1)	1.9 (1.6 to 2.3)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.1 (1.0 to 1.4)
Mediation effect (%)	-	2.0	Not same direction	22.4
PCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.8 (0.6 to 1.0)	1.9 (1.6 to 2.2)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.1 (0.9 to 1.3)	1.2 (1.0 to 1.4)
Mediation effect (%)	-	0.0	Not same direction	26.5
MCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.7 to 2.4)	0.9 (0.7 to 1.1)	2.2 (1.9 to 2.6)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)
Mediation effect (%)	-	0.0	Not same direction	Not same direction
Oral Pain Medications Use				
Direct, HR (95% CI) *	1.0 (reference)	2.0 (1.6 to 2.4)	0.9 (0.7 to 1.1)	2.1 (1.7 to 2.5)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)
Mediation effect (%)	-	3.9	Not same direction	12.0

n, number; OA, osteoarthritis; CI, confidence interval; HR, hazard ratio; PCS, physical component summary score;

MCS, mental component summary score; QoL, quality of life.

*Adjusted for age, race, sex, body mass index, education level, weekly alcohol consumption, smoking habits, history

of knee injury, comorbidities, depressive symptoms and widespread pain.

Table 4. Sensitive Analysis (OA Status Updated before Mediators)

	Neither Radiographic Knee OA nor Knee Pain (n=1,302)	Radiographic Knee OA Only (n=1,462)	Knee Pain Only (n=525)	Symptomatic Knee OA (n=1,209)
Number of Death	81	88	28	86
Deaths per 1000 Person-years (95% CI)	9.3 (7.4 to 11.5)	12.8 (10.3 to 15.7)	8.7 (5.8 to 12.5)	15.8 (12.6 to 19.5)
Total Effect, HR (95% CI)	1.0 (reference)	2.0 (1.5 to 2.7)	1.0 (0.6 to 1.5)	2.4 (1.8 to 3.3)
Total Effect, HR (95% CI) *	1.0 (reference)	1.7 (1.2 to 2.4)	0.9 (0.6 to 1.3)	2.0 (1.4 to 2.9)
Disability Score				
Direct, HR (95% CI) *	1.0 (reference)	1.7 (1.4 to 2.0)	0.6 (0.5 to 0.8)	1.1 (0.9 to 1.4)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.9 to 1.2)	1.4 (1.2 to 1.6)	1.7 (1.5 to 2.0)
Mediation effect (%)	-	2.4	Not same direction	85.5
PCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	1.7 (1.5 to 2.0)	0.7 (0.6 to 0.9)	1.6 (1.4 to 1.9)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.5)
Mediation effect (%)	-	0.0	Not same direction	38.9
MCS of QoL				
Direct, HR (95% CI) *	1.0 (reference)	1.7 (1.5 to 2.0)	0.8 (0.7 to 1.1)	2.0 (1.7 to 2.4)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)
Mediation effect (%)	-	2.4	Not same direction	0.0
Oral Pain Medications Use				
Direct, HR (95% CI) *	1.0 (reference)	1.7 (1.5 to 2.0)	0.8 (0.6 to 1.1)	1.9 (1.6 to 2.3)
Indirect, HR (95% CI) *	1.0 (reference)	1.0 (0.8 to 1.2)	1.1 (0.9 to 1.3)	1.1 (0.9 to 1.3)
Mediation effect (%)	-	2.4	Not same direction	11.4

n, number; OA, osteoarthritis; CI, confidence interval; HR, hazard ratio; PCS, physical component summary score;

MCS, mental component summary score; QoL, quality of life.

*Adjusted for age, race, sex, body mass index, education level, weekly alcohol consumption, smoking habits, history of knee injury, comorbidities, depressive symptoms and widespread pain.

Figure 1. A Directed Acyclic Graph to Describe the Mediation Effect between Symptomatic Knee OA and All-cause Mortality.

OA, osteoarthritis; PCS of QoL, physical component summary score of quality of life

Indirect effect: effect of symptomatic knee OA on all-cause mortality through its effect on mediators (i.e., disability and PCS of QoL)

Direct effect: effect of symptomatic knee OA on all-cause mortality not through its effect on mediators (i.e., disability and PCS of QoL)

Total effect: sum of indirect and direct effects

Confounders: confounders of association between symptomatic knee OA and all-cause mortality (i.e., age, race, sex, body mass index, education level, weekly alcohol consumption, smoking habits, history of knee injury, comorbidities, depressive symptom and widespread pain)

Direct Effect

Total Effect

Indirect Effect

Symptomatic Knee OA → Disability or Decreased PCS of QoL → **All-cause Mortality**

Confounders