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ORIGINAL ARTICLE

Does symptomatic knee osteoarthritis increase the risk of all-cause mortality? Data from four international population-based longitudinal surveys of aging

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Abstract

Objective This study aimed at examining the association between symptomatic knee osteoarthritis and all-cause mortality based on four population-based longitudinal surveys.

Method Data were retrieved from the English Longitudinal Study of Aging (ELSA), the Survey of Health, Aging and Retirement in Europe (SHARE), the Korean Longitudinal Study of Aging (KLoSA), and the Indonesian Family Life Survey (IFLS). The association between symptomatic knee osteoarthritis and all-cause mortality over the 8- to 12-year follow-up period was assessed using Cox-proportional hazard models.

Results In the entire sample of 59,522 participants (4823 with symptomatic knee osteoarthritis; 54,699 without symptomatic knee osteoarthritis [control group]; mean age: 61.8 years; female percentage: 55.3%), 8375 died (937 in the symptomatic knee osteoarthritis group, 7438 in the control group) during the follow-up period. Patients with symptomatic knee osteoarthritis had a higher risk of all-cause mortality than control group without adjusting for potential confounders in each survey, and the unadjusted hazard ratios (HRs) of all-cause mortality were 1.32 (95% confidence interval [CI] 1.18 to 1.47) in ELSA, 1.40 (95%CI 1.24 to 1.56) in SHARE, 1.25 (95%CI 1.06 to 1.47) in KLoSA, and 1.65 (95%CI 1.31 to 2.07) in IFLS. However, with adjustment of potential confounders, the corresponding HRs dropped to 1.07 (95%CI 0.94 to 1.20) in ELSA, 1.08 (95%CI 0.97 to 1.22) in SHARE, 0.91 (95%CI 0.77 to 1.08) in KLoSA, and 0.89 (95%CI 0.66 to 1.21) in IFLS, respectively.

Conclusions In these four population-based longitudinal studies, no association between symptomatic knee osteoarthritis and increased risk of all-cause mortality was observed after adjusting for potential confounders.

Key Points

- *This study evaluated the association between symptomatic knee OA and the risk of all-cause mortality among the participants retrieved from four large population-based longitudinal studies across the world.*
- *No association between symptomatic knee osteoarthritis and increased risk of all-cause mortality was observed after considering potential confounders, and our findings were consistent with the results derived from four independent longitudinal studies.*
- *The present study included four international population-based longitudinal studies, comprising both developed and developing areas, which allowed the findings to be interpreted under larger circumstance.*

Keywords Knee · Longitudinal studies · Mortality · Osteoarthritis

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Introduction

Osteoarthritis (OA) has been identified as a leading cause of disability in the elderly population [1, 2]. Approximately 50% of the global population aged ≥ 65 years were affected by OA [3]. Since OA has been associated with substantial joint pain, reduced joint function, and degraded quality of life, there seems to be a great importance to consider its impact on mortality [4–7]. In particular, pain might be the main motivator that drives excess mortality; this is fairly plausible since chronic pain has already been showed to be positively associated with mortality [8–11].

Earlier research works have investigated the association between symptomatic knee OA and mortality; the findings, however, are still inconclusive [12–16]. In addition, in order to concern the late effects of symptomatic knee OA on mortality, we can only use large database and a relatively long follow-up period to derive a more robust estimate of mortality and to identify its relationship with symptomatic knee OA [13]. To address this knowledge gap, this study aimed to evaluate the relation of symptomatic knee OA to the risk of all-cause mortality among the participants retrieved from four large population-based longitudinal studies across the world, with particular attention to addressing the potential sources of confounding bias which may account for the effect of knee OA on mortality.

Materials and methods

Data source

Surveys of aging are community-dwelling longitudinal studies and cross-national panel databases that largely focus on a variety of micro data of the nationally representative sample of the elderly population, including health condition, socioeconomic status, and social and family networks [17, 18]. In addition, these surveys are designed to ensure, to the maximum extent possible, comparability with other surveys, and their purposes of these surveys are usually to strengthen social relationship and improve people's life by providing users with seamless and flexible access to a wide range of data resources to facilitate high-quality research.

The sample of the present study was derived from four international surveys of aging: the English Longitudinal Study of Aging (ELSA), the Survey of Health, Aging and Retirement in Europe (SHARE), the Korean Longitudinal Study of Aging (KLoSA), and the Indonesian Family Life Survey (IFLS). The detailed design and other related information can be found from the websites of each survey (http://www.elsa-project.ac.uk/ [ELSA]; http://www.share-project.org/ [SHARE, covering 12 countries: Austria, Germany, Sweden, Spain, Italy, France, Denmark, Switzerland, Belgium, Greece, Netherlands, and Israel]; https://survey.keis.or.kr/eng/klosa/klosa01.jsp [KLoSA]; and https://www.rand.org/well-being/social-and-behavioral-policy/data/FLS/IFLS.html [IFLS]). The participants of these four longitudinal studies were recruited in the period of 2002–2007, and were interviewed on a range of physical health, lifestyle factors, and social status every 2 years for ELSA, SHARE, and KLoSA, or once in every 7 years for IFLS.

Ethical approval for all surveys were granted from the corresponding ethics committees: the Multicentre Research and Ethics Committee for ELSA, the Ethics Committee of the University of Mannheim for SHARE, the Seoul National University Hospital's Institutional Review Board for KLoSA, and the ethics review boards of RAND and University of Gadjah Mada in Indonesia for IFLS. All participants provided written informed consent to participate in these surveys.

Study population

Eligible participants included in the present analyses consisted of those who had information on symptomatic knee OA and death occurred during the follow-up period. Participants with any one of the following criteria were excluded: (1) incomplete records of covariates (i.e., age, height, weight, sex, education level, alcohol use, smoking status and comorbidities); (2) abnormal value of age (i.e., over 150 years old), height (i.e., less than 100 centimeters [cm] or larger than 200 cm) or weight (i.e., less than 30 kilograms [kg], or larger than 100 kg) at baseline. Further information on the selection process of participants for each cohort are shown in Online Resource 1.

Assessment of symptomatic knee OA

The fieldwork process of each cohort was carried out through personal interviews conducted by well-trained interviewers using computer-assisted personal interviewing or computer-assisted field editing [19–22]. The participants were firstly asked whether they were often bothered by joint pain in recent days. If they answered yes to this question, they would be further requested to specify at which joint such pain occurred. Then, the participants were expected to clarify whether they had been diagnosed with arthritis. Symptomatic knee OA was ascertained if a participant responded yes to both questions [23, 24]. Detailed information regarding the assessment of symptomatic knee OA among the included four studies are shown in Online Resource 2.

Assessment of mortality

The information on death that occurred during the follow-up visit was acquired from death certificate, field investigation, or proxy interview with a family member, neighbor, or friend of the deceased respondent or any other person close to the participant [25–28].

Assessment of covariates

The covariates were selected based on previous studies [13, 14, 16]. The information concerning age, sex, BMI, education level, and comorbidities were collected through standardized questionnaires completed during face-to-face interview. The data of height and body weight were self-reported, and BMI was calculated using the formula weight (kg)/height $(m)^2$. The education level was classified into three categories based on the highest level of education of the participant: elementary school or below, middle school, high school or above. The smoking status and alcohol use were recorded according to the self-reported history. Comorbidities were obtained from the participants based on their responses to whether they were informed of any health problem by the doctor, including hypertension, diabetes, heart diseases, chronic lung diseases, stroke, and cancer.

Statistical analysis

The continuous data were presented as means with standard deviations, and the categorical data were presented as number (percentages). The differences in sets of continuous data were evaluated either by *t* test (for normally distributed data) or Mann-Whitney *U* test (for non-normally distributed data), while the differences in sets of categorical data were evaluated by the Pearson Chi-square test. We determined person-years for each participant based on the length of time from the year of baseline visit to the year of the first occurrence of the following events: death, the most recent contact prior to the loss of follow-up, or the last follow-up visit. To deal with violations of positivity, which means participants at one or more levels of the confounders fail to receive at one or more levels of exposure, only the participants with age and BMI overlapping conditions were included in the current analysis for each dataset [29].

A total of three Cox-proportional hazard models were established using the time scale of age, and the hazard ratios (HRs) were calculated for the relationship between symptomatic knee OA and mortality: model 1, crude model; model 2, with adjustment of sex (male, female), age (continuous data), BMI (continuous data), education level (elementary school or below, middle school, high school or above), smoking status (yes or no), and alcohol use (yes or no); and model 3, with further adjustment of comorbidities (yes or no), including hypertension, diabetes, heart diseases, chronic lung diseases, stroke, and cancer on the basis of model 2.

All *P* values were 2-sided and $P < 0.05$ was considered significant for all tests. All analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA) and Stata V.14.1 (StataCorp LP., College Station, TX, USA) statistical packages.

Results

A total of 59,522 participants (26,603 men and 32,919 women) were included in the final analyses, and 4823 (8.1%) of them were diagnosed with symptomatic knee OA at the baseline visit. For each longitudinal study, the baseline characteristics of the included participants were presented in Table 1. Significant differences were observed between the participants with symptomatic knee OA and those without symptomatic knee OA (control group) in a number of covariates, such as age, sex, BMI, education level, smoking status, and alcohol use. Furthermore, the participants with symptomatic knee OA tended to exhibit more comorbidities, including hypertension, diabetes, heart diseases, chronic lung diseases, and stroke, than the control group in general.

As shown in Table 2, a total of 8375 participants died during the 8- to 12-year follow-up period. Of them, 937 occurred among the participants with symptomatic knee OA and 7438 in the control group. The all-cause mortality rate was found to be higher in participants with symptomatic knee OA (ELSA 27.7 per 1000 person-years; SHARE 18.6 per 1000 person-years; KLoSA 18.7 per 1000 person-years; IFLS 25.8 per 1000 person-years) than in the control group (ELSA 20.5 per 1000 person-years; SHARE 13.0 per 1000 person-years; KLoSA 14.8 per 1000 person-years; IFLS 15.1 per 1000 person-years). For the comparison of symptomatic knee OA and the control group of each cohort, the crude HRs for all-cause mortality were 1.32 (95% confidence interval [CI] 1.18 to 1.47) in ELSA, 1.40 (95% CI 1.24 to 1.56) in SHARE, 1.25 (95% CI 1.06 to 1.47) in KLoSA, and 1.65 (95% CI 1.31 to 2.07) in IFLS (model 1).

However, when considering sex, age, BMI, education, smoking status, and alcohol use as confounders (model 2), the above positive associations became much weaker or disappeared (ELSA HR = 1.12, 95% CI 0.99 to 1.25; SHARE HR = 1.12, 95% CI 1.00 to 1.26; KLoSA HR = 0.92, 95% CI 0.78 to 1.10; IFLS HR = 1.01, 95% CI 0.75 to 1.37). In addition, with further adjustment of comorbidities on the basis of model 2, the positive association was no longer valid in any of the longitudinal studies, as suggested by the results of model 3. The corresponding multivariable-adjusted HRs were 1.07 (95% CI 0.94 to 1.20) in ELSA, 1.08 (95% CI 0.97 to 1.22) in SHARE, 0.91(95% CI 0.77 to 1.08) in KLoSA, and 0.89 (95% CI 0.66 to 1.21) in IFLS.

Discussions

Using data collected from four international population-based longitudinal surveys covering 15 countries, this study revealed that symptomatic knee OA was not associated with increased risk of all-cause mortality after adjusting for some

Table 1 Characteristics of the participants stratified by symptomatic knee osteoarthritis status at baseline

Characteristics	ELSA (2002–2012)		SHARE (2004–2015)		KLoSA (2006–2014)		IFLS (2007–2015)	
	SKOA ($n = 1529$)	Non-SKOA ($n = 9322$)	SKOA ($n = 1710$)	Non-SKOA ($n = 26823$)	SKOA ($n = 1166$)	Non-SKOA ($n = 8754$)	SKOA ($n = 418$)	Non-SKOA ($n = 9800$)
Female, *n* (%)	972 (63.6)	5066 (54.3)	1252 (73.2)	14704 (54.8)	991 (84.5)	4557 (52.1)	304 (72.7)	5073 (51.8)
Age, year (Mean ± SD)[a]	66.4 ± 10.3	63.7 ± 10.9	67.7 ± 10.2	63.7 ± 10.4	67.8 ± 9.4	60.5 ± 10.8	60.3 ± 11.1	53.2 ± 10.6
BMI, kg/m^2 (Mean ± SD)[a]	29.1 ± 4.8	27.2 ± 4.2	27.1 ± 4.2	25.9 ± 3.7	23.6 ± 3.2	23.1 ± 2.8	24.1 ± 4.6	23.0 ± 4.0
Education, *n* (%)								
Elementary school or below	835 (54.7)	3631 (38.9)	263 (15.4)	3257 (12.1)	872 (74.8)	3501 (40.0)	232 (73.7)	4904 (60.5)
Middle school	280 (18.3)	2032 (21.8)	996 (58.2)	16126 (60.2)	156 (13.3)	1573 (18.0)	37 (11.8)	1094 (13.5)
High school or above	414 (27.0)	3659 (39.3)	451 (26.4)	7440 (27.7)	138 (11.9)	3680 (42.0)	46 (14.5)	2114 (26.0)
Alcohol use, *n* (%)								
No	668 (43.7)	2738 (29.4)	626 (36.6)	8389 (31.3)	911 (78.1)	5281 (60.3)	–	–
Yes	861 (56.3)	6584 (70.6)	10846 (63.4)	18434 (68.7)	255 (21.9)	3473 (39.7)	–	–
Smoking, *n* (%)								
No	508 (33.2)	3480 (37.3)	1067 (62.4)	14026 (52.3)	1019 (87.4)	6030 (68.9)	305 (73.0)	5840 (59.6)
Yes	1021 (66.8)	5842 (62.7)	643 (37.6)	12797 (47.7)	147 (12.6)	2724 (31.1)	113 (27.0)	3960 (40.4)
Comorbidities, *n* (%)								
Hypertension	700 (45.8)	3259 (34.9)	726 (42.5)	8119 (30.3)	516 (44.3)	2209 (25.2)	171 (40.9)	1739 (17.7)
Diabetes	146 (9.6)	602 (6.5)	206 (12.1)	2537 (9.5)	220 (18.9)	963 (10.9)	26 (6.2)	292 (3.0)
Heart diseases	113 (7.4)	490 (5.3)	280 (16.3)	3177 (11.8)	105 (9.0)	376 (4.3)	3 (0.7)	65 (0.7)
Chronic lung diseases	163 (10.7)	515 (5.5)	164 (9.5)	1202 (4.5)	39 (3.3)	175 (2.0)	21 (5.0)	213 (2.2)
Stroke	84 (5.5)	347 (3.7)	75 (4.4)	978 (3.7)	–	–	7 (1.7)	44 (0.5)
Cancer	101 (6.6)	555 (5.9)	109 (6.4)	1422 (5.3)	25 (2.1)	209 (2.4)	2 (0.5)	42 (0.4)

n number, *SD* standard deviation, *SKOA* symptomatic knee osteoarthritis, *ELSA* English Longitudinal Study of Aging (2002–2012), *SHARE* Survey of Health, Aging and Retirement in Europe (2004–2015), *KLoSA* Korean Longitudinal Study of Ageing (2006–2014), *IFLS* Indonesian Family Life Survey (2007–2015)

[a] The age overlap is 35–99 years old in ELSA, 41–99 years old in SHARE, 45–92 years old in KLoSA, and 40–96 years old in IFLS; the BMI overlap is 17.19–41.91 kg/m^2 in ELSA, 16.00–40.00 kg/m^2 in SHARE, 13.33–38.40 kg/m^2 in KLoSA, and 16.02–37.49 kg/m^2 in IFLS

major potential confounders, including age, sex, BMI, education, smoking status, alcohol use, and comorbidities.

The association between OA and mortality has been investigated previously; the findings, however, are still inconclusive. For example, a systematic review published in 2008 reported that patients with OA were subject to a higher mortality than the general population, supported by moderate evidence [30]. In 2016, a meta-analysis was conducted to explore the association between OA and the risk of all-cause mortality [3], and the results suggested that no significant association between symptomatic OA and increased risk of mortality was confirmed; however, the authors acknowledged that the association between symptomatic knee OA and mortality remained unclear in view of the limited number of studies restricting to knee joint and the relatively low quality of included studies [3].

The findings of this study are consistent with some of the earlier studies [12, 13, 24, 31]. A prospective cohort study based on data extracted from the Genetics ARthrosis and Progression (GARP) study and the Osteoarthritis Care Clinic (OCC) study reported that no association between symptomatic knee OA and increased risk of all-cause mortality was confirmed in a model with adjustment of age and sex [12]. Another cohort study targeting at the Swedish population also did not observe any increase in mortality in patients of physician-diagnosed knee OA after adjusting for sex, year of first health-visit, socioeconomic status, and comorbidities [13]. In addition, a study conducted in a cohort representative of the US population (i.e., the National Health and Nutrition Examination Surveys) found no increase in the risk of all-cause mortality associated with the self-reported and radiographic knee OA as well [24]. Furthermore, a meta-analysis and prospective cohort study (i.e., the Progetto Veneto Anziani study) conducted by Veronese et al. also failed to show a statistically significant association between knee OA and all-cause mortality [31]. However, a community-based prospective cohort study targeting at the African American and Caucasian populations showed a 13% increase in the risk

Table 2 Association between symptomatic knee osteoarthritis and all-cause mortality

	ELSA (2002–2012)		SHARE (2004–2015)		KLoSA (2006–2014)		IFLS (2007–2015)	
	SKOA	Non-SKOA	SKOA	Non-SKOA	SKOA	Non-SKOA	SKOA	Non-SKOA
Participants (*n*)	1529	9322	1710	26823	1166	8754	418	9800
Death (*n*)	375	1738	319	3593	164	986	79	1121
Mortality rate (per 1000 person-years)	27.73	20.47	18.58	13.02	18.68	14.78	25.76	15.08
Model 1, HR (95% CI)	1.32 (1.18,1.47)	1.00 (reference)	1.40 (1.24, 1.56)	1.00 (reference)	1.25 (1.06, 1.47)	1.00 (reference)	1.65 (1.31, 2.07)	1.00 (reference)
Model 2, HR (95% CI)	1.12 (0.99, 1.25)	1.00 (reference)	1.12 (1.00, 1.26)	1.00 (reference)	0.92 (0.78, 1.10)	1.00 (reference)	1.01 (0.75, 1.37)	1.00 (reference)
Model 3, HR (95% CI)	1.07 (0.94, 1.20)	1.00 (reference)	1.08 (0.97, 1.22)	1.00 (reference)	0.91 (0.77, 1.08)	1.00 (reference)	0.89 (0.66, 1.21)	1.00 (reference)

n number, *HR* hazard ratio, *SKOA* symptomatic knee osteoarthritis, *ELSA* English Longitudinal Study of Aging (2002–2012), *SHARE* Survey of Health, Aging and Retirement in Europe (2004–2015), *KLoSA* Korean Longitudinal Study of Ageing (2006–2014), *IFLS* Indonesian Family Life Survey (2007–2015)

Model 1: crude HR; Model 2: adjusted by sex, age, BMI, education level, smoking status and alcohol use (sex, age, BMI, education, smoking for the IFLS); Model 3: further adjusted by hypertension, diabetes, cancer, chronic lung diseases, heart diseases, and stroke on the basis of model 2 (hypertension, diabetes, cancer, chronic lung diseases and heart diseases for the KLoSA)

of all-cause mortality in patients of systematic knee OA [14]. Another study using data collected from the prospective community-based Chingford Cohort Study observed a significant increase in the risk of all-cause mortality in female participants who had experienced knee pain with or without radiographic OA [15]. Similarly, the Wuchuan OA Study including the Chinese rural population reported a positive association between symptomatic knee OA and all-cause mortality [16]. In addition, another cohort study conducted by Tsuboi et al. also found that subjects with radiographic knee OA experienced a higher risk of mortality than those without radiographic knee OA [32]. The present study by using four large population-based longitudinal surveys covering 15 countries further showed that symptomatic knee osteoarthritis may not increase the risk of all-cause mortality after adjusting for potential confounders.

Several strengths of the present study are noteworthy. First of all, it included four international population-based longitudinal studies, comprising both developed and developing areas, which allowed the findings to be interpreted under larger circumstance. Secondly, our findings were consistent with the results derived from four independent longitudinal studies, suggesting that the observed associations appear valid.

The limitations of this study should be highlighted as well. First, the participants in these four longitudinal studies did not undergo radiographic assessment. The diagnosis of symptomatic knee OA was merely dependent on self-reported information on knee pain and diagnosis by a physician, and validation of this definition was not clear in these datasets. Thus, there likely was some misclassification of symptomatic knee OA. Such bias, if occurred, might dilute the observed association toward the null. Nevertheless, diagnosis of OA based on self-reported questionnaires has been preferred by many previous studies [23, 24]. In addition, while various rheumatic diseases can cause knee pain, the prevalence of OA in the middle-aged and old population is much higher than the prevalence of other rheumatic diseases, e.g., rheumatoid arthritis [33, 34]. Thus, a majority of knee pain is likely to be caused by knee OA. Finally, we believe symptomatic knee OA is a more important disease phenotype from the public health point view as Zhang and colleague pointed out that OA community should shift gears in OA research toward symptomatic OA [35]. Second, residents in rural areas may be less likely to visit a physician and may not aware of some comorbidities which are asymptomatic for a long time (i.e., hypertension, diabetes); thus, the prevalence of these comorbidities may be underreported. However, considering patients with symptomatic knee OA have a higher chance of having comorbidities (e.g., hypertension and diabetes) compared with the control group [36], such underreporting, if it existed, may bias the effect of symptomatic knee OA on mortality away from the null. Since our study showed that there was no statistically significant association between symptomatic knee OA and all-cause mortality after adjusting for potential covariates (e.g., comorbidities), the potential underreporting of comorbidities, if existed, should not substantially change our conclusion. Third, individual-level alcohol data was not collected in IFLS, which might have some impact on the associations. However, approximately 90% participants in the IFLS dataset are Muslims. As the largest Islam state in the world, alcohol consumption is religiously restricted and legal measures to reduce alcohol consumption are well-implemented, which in turn make Indonesia a country among the locations of lowest drinking prevalence [37, 38]. In addition, over 98% households did not

purchase, self-produce, or receive any alcoholic beverage during the week before the interview in the IFLS dataset. Furthermore, the results from other three datasets with alcohol data were all consistent after adjusting for the alcohol use status. Thus, the lack of alcohol data in IFLS may not affect our study findings materially. Fourth, we were unable to evaluate the cause of death as the relevant data were not collected in the four longitudinal surveys of aging. Comprehensive investigation on cause-specific death, such as death due to cardiovascular diseases, would provide valuable information for developing specific measures to lower the resulted mortality.

Conclusions

In these four population-based longitudinal studies, no association between symptomatic knee osteoarthritis and increased risk of all-cause mortality was observed after considering potential confounders.

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Authors' contributions YX and TY are joint corresponding authors. ZY, YX, and TY conceived the study. ZY, YX, and TY were responsible for conception of the study and drafted the manuscript. GL, YX, and TY were responsible for design of the study. XL, ZX, XZ, YH, contributed to preparation and data analysis. YW, TY, YX, and GL contributed to revision of the manuscript. 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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Data availability The datasets during the current study available from the websites of each survey on reasonable request.

Compliance with ethical standards

Ethical approval for all surveys were granted from the corresponding ethics committees: the Multicentre Research and Ethics Committee for ELSA, the Ethics Committee of the University of Mannheim for SHARE, the Seoul National University Hospital's Institutional Review Board for KLoSA, and the ethics review boards of RAND and University of Gadjah Mada in Indonesia for IFLS. All participants provided written informed consent to participate in these surveys.

Disclosures None.

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