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Original Article

Association between osteoarthritis and mortality: a meta-analysis

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Abstract: Current evidence finds that the role of osteoarthritis (OA) on mortality remains controversial. Therefore, we conducted a meta-analysis to determine whether the association between OA and all-cause mortality as well as cardiovascular disease (CVD) related mortality exists. We searched the Pubmed, Embase and Cochrane Library databases, and identify cohort studies to evaluate the association between OA and mortality. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using random effects model. Subgroup analyses were performed to investigate potential sources of heterogeneity, and Stata 11.0 was used to analyze data. A total of 12 articles, involving 13 studies, were included in this meta-analysis. We did not find a statistically significant association between OA and all-cause mortality (RR = 1.06; 95% CI 0.89 to 1.28), and there was evidence of high heterogeneity of RRs across these studies (I^2 = 94.4%, P<0.001). However, when the studies were stratified by definition of mortality, a significant association was shown between OA and CVD mortality (RR = 1.36; 95% CI 1.10 to 1.69) with decreased heterogeneity (I^2 = 70.2%, P = 0.01). People with OA showed an increased risk of CVD related mortality although the association with overall mortality was less clear. However, additional high quality research is still required to further explore the relationship between OA and all-cause as well as specific-cause mortality.

Keywords: Osteoarthritis, mortality, cardiovascular, systematic review, meta-analysis

Introduction

Osteoarthritis (OA), as a common disease in middle-aged and elderly people, is associated with severe joint pain and reduced function as well as quality of life [1]. Due to the rapidly growing and ageing populations paralleled with the increasing prevalence of obesity, it is anticipated that the number of people with OA will continue to rise in the future [2, 3]. As a result, OA is expected to impose a significant burden to the health economy [4].

As we know, both rheumatoid arthritis and OA are associated with substantial joint pain and reduced function in populations worldwide [5, 6]. Though there is ample evidence of increased mortality in patients with rheumatoid arthritis in comparison with the general population [7, 8], the relationship between OA and mortality is less clear. In the year of 2008, Hochberg make a systematic review and concluded that there was moderate evidence of increased mortality among people with OA compared with the general population [9]. On the other hand, the meta-analysis conducted by Xing et al revealed that there is no reliable and confident evidence existed in respect of the association between OA and mortality [10]. However, both of the two studies were limited by the shortage of sufficient evidence, and after their reports, some studies have been published in recent years which may be useful for arriving at clinical recommendations. Thus, the aim of the current study was to systematically review all available literature and perform a comprehensive meta-analysis to determine whether people with OA present a differential risk of overall and cardiovascular disease (CVD) mortality than those without OA.

Materials and methods

Data sources and searches

This meta-analysis was performed in accordance with the Meta-analysis of Observational

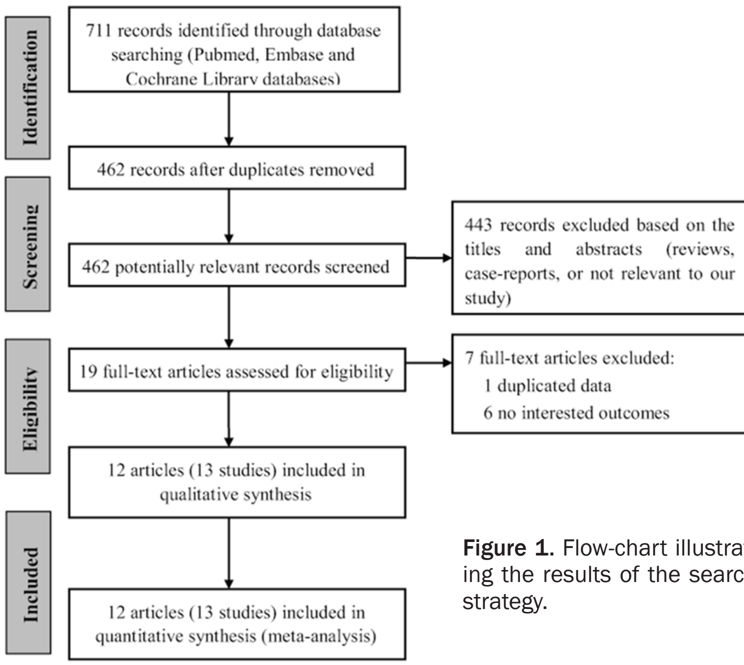

Figure 1. Flow-chart illustrating the results of the search strategy.

Studies in Epidemiology (MOOSE) statement [11]. We searched Pubmed, Embase, and the Cochrane Library databases from their inception to July 1, 2016, and identified studies that evaluated the association between OA and mortality in human populations without language restriction. MeSH terms "osteoarthrosis" and "mortality", and their corresponding free terms were used to search relevant studies. We also scanned the cited references of retrieved articles to identify any potentially eligible studies.

Study selection criteria

A published article was included if it (1) had a cohort study design, (2) evaluated the association between OA and risk of death, and (3) reported the risk ratios (RRs) or hazard ratios (HRs) and their 95% confidence intervals (CIs). If publications were duplicated or articles from the same study population, the most informative publication was included. Studies were excluded if they were not relevant to our study, or did not provide available data.

Data extraction

Data were independently extracted by two investigators and checked by the other authors, and any discrepancies were resolved by consensus. The following information was abstracted from all included publications: name of first author, publication year, country, age of subjects, sex of patients, anatomical location, length of follow-up and definition of OA. Estimates were either retrieved directly from the article or calculated from available data. When available, we used the most comprehensively adjusted estimates.

In the included studies, Kellgren Lawrence (KL) grade system (range 0-4) was used to evaluate the radiography of joint [12]. Radiographic OA was defined as having a KL grade ≥2, and symptomatic OA was having radiographic OA as well as joint pain. Besides, all-cause mortality was used as the main investigated result except where otherwise specified.

Assessment of methodological quality

We applied the Newcastle-Ottawa Scale (NOS) to evaluate the reporting rigor of observational studies [13]. The NOS system is a scoring check-list addressing issues of design, in which it included issues of selection of participants and comparability of exposure as well as outcomes. Studies awarded six or more stars were considered of high quality and were analyzed.

Statistical analysis

RRs and 95% CIs were used to present the association between OA and mortality. Random-effects model was used to calculate the estimates because significant heterogeneity was anticipated across included studies, and results from the random-effects model are usually more conservative than the fixed-effects one. The distribution of combined RRs and their 95% CIs were represented using forest plots. The Cochran Q test was used to estimate the *P* value for heterogeneity. We also calculated the I^2 statistic to assess heterogeneity across studies, using the following interpretation: I^2<50% was considered low heterogeneity; I^2 of 50%-75% means moderate heterogeneity; and I^2> 75% was considered high heterogeneity. Sen-

Table 1. Basic characteristics of included studies

Name of first author	Publication year	Country	Year of survey	No. of total subjects	Age of subjects (years)	Sex	Mortality	Anatomy location	Definition of OA	Length of follow-up	RR (95% CI)	Adjustment	NOS score
Holbrook	1990	United States	1974-1986	519	≥50	Men/women	All cause/ cardiovascular	Knee, back, hand, hip	Self-reported	10 years	0.83 (0.51-1.36)	Yes	6
Haara	2003	Finland	1978-1994	3,595	≥30	Men/women	All cause/ cardiovascular	Hand	Medical history, symptoms, and physical examination	15-17 years	1.07 (0.90-1.27)	Yes	8
Nuesch	2011	England	1994-2009	1,163	≥35	Men/women	All cause/ cardiovascular	Knee, hip	Radiographic	14 years	1.55 (1.41-1.70)	Yes	8
Tsuboi	2011	Japan	1997-2007	789	≥60	--	All cause	Knee	Radiographic	10 years	2.32 (1.41-3.80)	Yes	7
Cacciatore	2014	Italy	1992-2004	1,332	≥65	--	All cause	Joints	Symptom and physical examination	12 years	1.28 (0.98-1.39)	Yes	7
Barbour	2015	United States	1988-2013	9,704	≥65	--	All cause/ cardiovascular	Hip	Radiographic	16.1 years	1.24 (1.13-1.35)	Yes	7
Haugen	2015	United States	1990-2011	5,209	≥50	--	All cause	Hand	Symptomatic/ radiographic	--	0.79 (0.57-1.10)	Yes	8
Kluzek	2015	United Kingdoms	1993-2014	1,629	≥45	--	All cause/ cardiovascular	Knee/hand	Symptomatic/ radiographic	21.7 years	1.43 (0.77-2.65)	Yes	8
Liu Rani (GARP)	2015	Netherlands	2000-2011	383	--	Men/women	All cause/ cardiovascular	Hand/knee/ hip/spine	Symptomatic	9.9 years	0.54 (0.37-0.79)	No	6
Liu Rani (OCC)	2015	Netherlands	2005-2011	459	--	Men/women	All cause	Hand/knee/ hip	--	3.9 years	0.45 (0.25-0.82)	No	6
Liu Q	2015	China	2005-2013	1,025	≥50	--	All cause	Knee	Symptomatic/ radiographic	8 years	1.9 (1.0-3.5)	Yes	7
Turkiewicz	2016	Sweden	1998-2012	524,136	≥45	Men/women	All cause	Hip/knee	ICD-10	10.3 years	0.88 (0.86-0.91)	Yes	7
Veronese	2016	Italy	1995-2001	2,927	≥65	--	All cause	Hand/hip/ knee	Symptomatic	4.4 years	0.95 (0.77-1.15)	Yes	8

OA, osteoarthritis; RR, risk ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale; ICD, international classification of diseases.

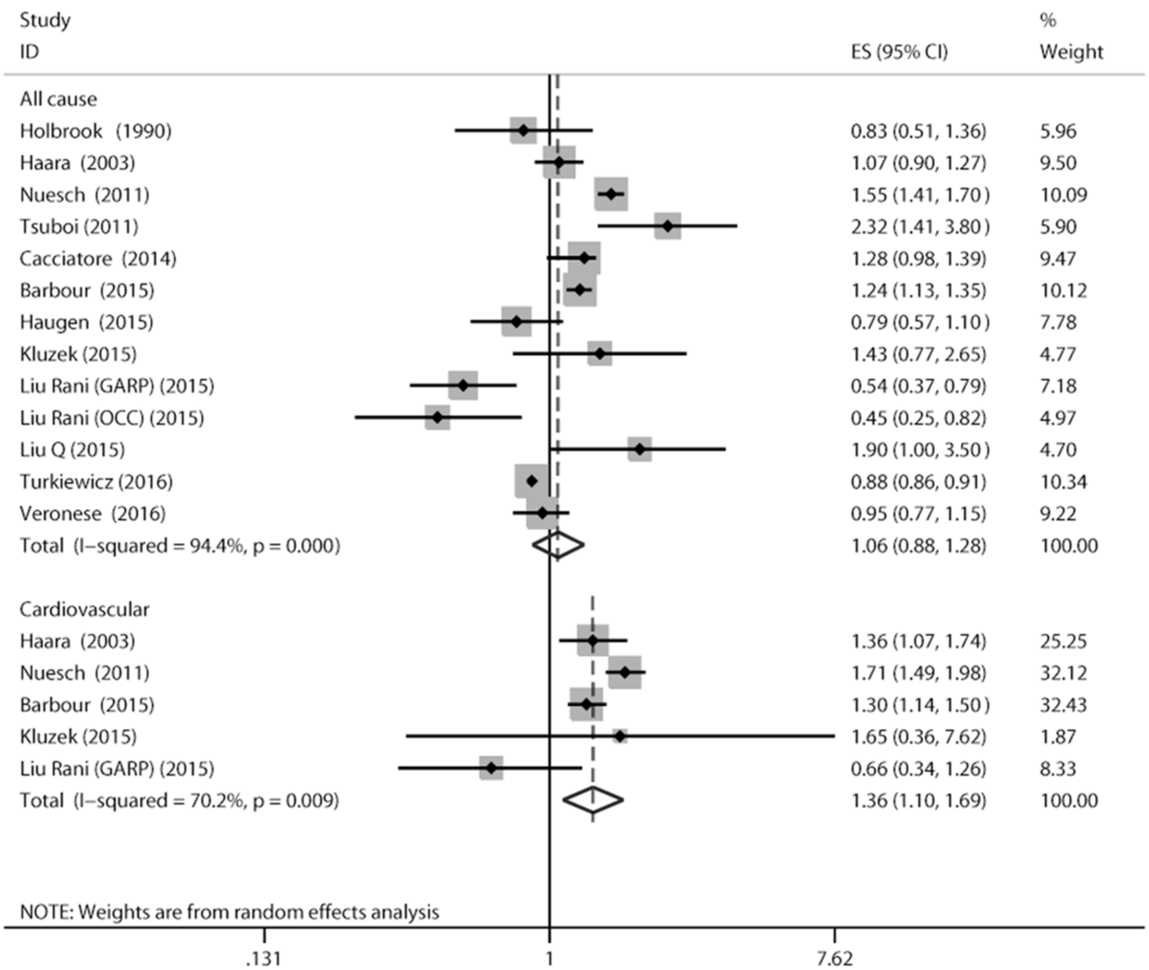

Figure 2. Forrest plots showing associations of osteoarthritis with all cause and cardiovascular-specific mortality.

sitivity analyses were performed to test the robustness of overall estimate. We also conducted subgroup analyses to investigate potential sources of heterogeneity.

Publication bias was assessed with a combination of the Egger test and Begg test. We used STATA, version 11.0 (Stata Corp) for all analyses. All statistical tests were two-sided and *P* values <0.05 was considered to be statistically significant.

Results

Literature search results

With the search strategy, 711 citations were initially retrieved. Of these, 249 records were duplicates. After review of the titles and abstracts, 443 articles were irrelevant records and 19 were considered of interest and full text was retrieved for detailed evaluation. After that, seven articles were further excluded and ultimately 12 articles [14-25], involving 13 studies, were included in this meta-analysis (**Figure 1**).

Study characteristics

Thirteen independent cohort studies were published between 1990 and 2016. Of all the studies, 8 studies were conducted in Europe, 3 in North America, and the other 2 in Asia. Thirteen studies investigated all-cause mortality, and 5 studies reported CVD mortality. According to the NOS system, 5 studies were awarded 8 stars, 5 studies were awarded 7 stars, and 3 studies were awarded 6 stars. Detailed information on study characteristics is shown in **Table 1**.

Table 2. Subgroup analyses of pooled risk ratios and heterogeneity analyses

Stratified factors	No. of studies	RRs	95% CIs	*P* value	I^2 (%)	*P* value for I^2
Sex						
Men	5	1.02	0.73-1.43	0.91	94.1	<0.001
Women	5	0.86	0.60-1.24	0.42	94.9	<0.001
Definition of mortality						
All cause	13	1.06	0.89-1.28	0.51	94.4	<0.001
Cardiovascular	5	1.36	1.10-1.69	0.01	70.2	0.01
Anatomy location						
Knee	6	1.24	0.87-1.76	0.23	84.5	<0.001
Hip	4	1.06	0.77-1.20	0.65	93.6	<0.001
Hand	4	1.01	0.89-1.14	0.94	0	0.46
Definition of OA						
Symptomatic	5	0.95	0.68-1.33	0.76	74.1	0.004
Radiographic	6	1.24	1.01-1.53	0.04	85.3	<0.001

RRs, risk ratios; CIs, confidence intervals; OA, osteoarthritis.

OA and mortality

In this meta-analysis, we did not find a statistically significant association between OA and all-cause mortality (RR = 1.06; 95% CI 0.89 to 1.28), and there was evidence of high heterogeneity of RRs across these studies (I^2 = 94.4%, P<0.001) (**Figure 2**).

Sensitivity analysis, in which the meta-analyses were serially repeated after exclusion of each study, showed that the RR values ranged from 1.01 to 1.11, but no individual study affected the significant difference of the overall RR. Among the included studies, 2 studies had unadjusted RR values, 3 studies had 6 stars of NOS system, and 4 studies had sample size less than 1,000. After exclusion of these studies serially, any of the combined RRs did not materially change.

In the analysis of publication bias, neither the Egger test nor the Begg test showed evidence of significant publication bias (Egger, P = 0.24; Begg, P = 0.67).

Subgroup analysis

We also performed stratified analyses across a number of key study characteristics. When the studies were stratified by definition of mortality, the *P* value showed no statistically significant in all-cause mortality group, but there was a significant association between OA and CVD mortality (RR = 1.36; 95% CI 1.10 to 1.69) with decreased heterogeneity (I^2 = 70.2%, P = 0.01) (**Figure 2**). Similarly, when the studies were stratified by definition of OA, there was an association between radiographic OA and all-cause mortality (RR = 1.24; 95% CI 1.01 to 1.53) with decreased heterogeneity (I^2 = 74.1%, P = 0.004), although the pooled estimates evaluating symptomatic OA showed no significant association with all-cause mortality (**Table 2**).

Discussion

Twelve publications, involving 13 prospective cohort studies, have examined the association between OA and risk of death. In the present meta-analysis, we did not find a statistically significant association between OA and all-cause mortality, which means that people with OA do not have significantly higher prevalence of overall mortality. However, we found that individuals with OA were more likely to experience CVD mortality in comparison with normal people.

All-cause mortality is a major area of research in OA. Patients with OA could die of different kinds of disease, such as CVD disease, cancer, gastrointestinal disease, and other causes. Analyzing mortality from specific disease was more reasonable to give clinical recommendation. CVD diseases such as stroke and myocardial infarction are a leading cause of mortality in OA patients [26]. In consistent with the study conducted by Veronese et al [25], people with OA were found to be at an increased risk of CVD-specific mortality though the association with overall mortality is less clear. People with OA are known to have high incidence of CVD disease [26], increased inflammatory profile [27] and low levels of physical activity [28], any of these reasons may predispose people with OA to premature mortality due to CVD disease. However, it was impossible to determine a definite causal relationship between OA and CVD mortality yet. Further longitudinal studies are still needed to inform how this occurs and whether there is a causal relationship over a sufficient study period. Besides, the association between OA and cancer-cause mortality also need to be examined if sufficient studies were available in the future.

Symptomatic and radiographic OA may have different effect on the risk of all-cause mortality. In a study conducted by Xing et al, the authors found that patients with symptomatic OA are likely to suffer from physical disability, and lack of walking disability is one of the risk factors for death [10]. However, our result in this meta-analysis was contrary from their study. Radiographic OA was shown to be associated with all-cause mortality, while symptomatic OA was not. However, this result was not robust (*P* = 0.04), which means that the difference could be a result of low statistical power, and thus further research on this topic is obviously needed.

We hypothesized that some degree of clinical heterogeneity might be induced by the different anatomical location, and thus made a subgroup analysis according to joint-specific OA. Our results showed that hip, knee, or hand OA was not associated with mortality. In a previous study by Veronese et al [25], the authors concluded that hip or knee OA did not predict early death, but there was a trend towards a significant reduction in mortality for hand OA. Our result did not support the statement that there was a negative association between hand OA and mortality, and we think that the relatively small number of included studies in their meta-analysis may result in a false positive result.

Strengths of this meta-analysis include the strict inclusion criteria, the relatively large number of sample size, and the robustness of the findings in sensitivity analyses. The absence of significant publication bias supports the robustness of the study findings. However, there are several limitations in this meta-analysis. First, although subgroup analyses were performed, none of the analyzed factors was able to explain all the heterogeneity. As there were considerable differences across studies, like age of subjects or length of follow-up, these differences might result in an increased heterogeneity and have an effect on the final results. Second, the results of included studies were adjusted for various factors. We have to confess that difference in levels of adjustment is another main source of heterogeneity. Third, though CVD mortality was investigated, we did not make a further subgroup analysis because of the numbers of studies investigating CVD mortality was relatively small. Further research that examines the association between OA and CVD mortality are still required in the future.

In spite of the limitations mentioned above, this study is clinically valuable to some extent. In summary, it appears that people with OA are at increased risk of CVD-specific mortality though the association with overall mortality is less clear. Anyhow, additional prospective research is still required to further explore the relationship between OA and all-cause as well as specific-cause mortality.

Disclosure of conflict of interest

None.

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