Mortality and other outcome measures in osteoarthritis

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Chapter 7

Mortality in osteoarthritis: a systematic review

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Submitted

ABSTRACT

OBJECTIVE

To summarize and to determine the association between osteoarthritis (OA) and mortality in three clinical settings: patients undergoing arthroplasty or seeking care for their OA or persons in the general population.

METHODS

A systematic search was performed up to October 2016. Two independent reviewers identified studies that reported mortality for OA patients, compared with a non-OA population. Study quality was also assessed. Information on study design, patient characteristics, OA status, duration of follow-up, mortality assessment and mortality rates were extracted for each study. Meta-analysis was performed when appropriate.

RESULTS

Of 5121 individual references, 33 articles reporting on 35 studies including 499103 participants were selected.

Seven high quality joint arthroplasty studies reported either an equal or reduced overall mortality rate for OA patients when compared to the general population.

Two high quality studies of OA patients seeking care reported no association between OA and mortality.

Results of ten population-based studies of high quality were equivocal. Some studies found a positive association between OA and mortality, while others did not. Meta-analysis of 6 studies showed no association. (HR 1.04 (95% Confidence Interval 0.91-1.18)). The association may depend on OA subtype.

CONCLUSION

There is no clear association between the presence of OA and mortality.

INTRODUCTION

Osteoarthritis (OA) is a common disease and its prevalence is rising. It has been estimated that more than 40 million of European adults suffer from symptomatic OA.[1] OA often results in pain, disability and decreased quality of life.[2] Whether OA also results in increased mortality is currently not clear.

Evidence concerning mortality due to OA is contradictory. One narrative review and two systematic reviews have broached this topic.[3-5] Unfortunately, these reviews had some shortcomings. In the narrative review the search for evidence was not systematically performed, so relevant and valid studies could have been missed.[3,6] The systematic reviews focused on mortality risk estimates (hazard ratios (HR)), did not include studies that classified OA based on total joint replacement surgery, [4] or only included studies when radiographic OA was present.[5] Furthermore, several new studies on this subject have been published.[7,8]

Therefore, we conducted a systematic review to summarize and to determine the association between OA and mortality for three different settings, i.e., the general population, among patients with OA requiring a total joint replacement, and among patients seeking health care for their OA complaints.

METHODS

Identification of studies

A systematic search (up to October 2016) was performed with a medical librarian in the databases PubMed, Embase, COCHRANE Library, Web of Science, ScienceDirect, CINAHL and Academic Search Premier (see supplementary Appendix I for a detailed overview of the search strategy). Reference lists of included studies were screened to identify additional relevant studies and articles could also added by hand search.

Inclusion and exclusion criteria

Two reviewers (RL and MK) performed the selection of titles, abstracts and full text articles, independently of each other. The exclusion of full text articles and thus selection of articles for inclusion in this review was performed by two independent reviewers (by either RL and MK or RL and MCK). Disagreements were resolved by discussion in consensus meetings. Studies which reported overall mortality in primary OA patients, when compared with a non-OA or general population, were included. Case reports, case series, (meeting) abstracts, reviews, studies investigating other musculoskeletal disease than primary OA and studies in other languages besides English and Dutch were excluded. Studies solely using diseases

with an established increased mortality rate as control groups, e.g. rheumatoid arthritis, were also excluded. Follow-up of at least a year was required to distinguish OA related mortality from mortality as a part of postoperative complications. If multiple publications occurred of the same study, the publication with the largest or most recent analysis was selected.

Data extraction

Information on OA demographics (population size, patient characteristics, age, sex) and duration of follow-up were extracted for each study. We only extracted mortality data for OA patients. In case more than one control group was used, the general population group was chosen if present.

Assessment of study quality

Study quality was assessed by RL and MCK using 14 criteria based on previous systematic reviews in the field of musculoskeletal disorders.[9,10] The criteria were modified to evaluate studies on the association between OA and mortality (see supplementary Appendix II). When a criterion was met in the article, '1' was given, otherwise '0'. A '0' was also given when incomplete or no information was given about the specific criterion or if information was not provided for the OA patients separately. The maximum score obtainable for cohort studies was 10, for nested case-control studies 13. For each study, the total quality score was calculated as the percentage of the maximum score obtainable. A study was rated as a high quality study if ≥67% was scored.

Data analysis

To investigate the association between population based OA studies and mortality, a meta-analysis was performed. The HRs of high quality studies were pooled using a random effect model to account for heterogeneity of the studies. Subgroup analyses were performed for different OA subtypes (knee, hip, hand). If different radiographic scoring systems were used to define OA, the HR based on the most often used was included in the meta-analysis. Additionally, a sensitivity analysis was performed by analyzing radiographic and symptomatic OA separately. All analyses were done using Stata V14 (StataCorp LP, Texas).

RESULTS

Selection of studies

The electronic databases yielded 5121 individual references of which 1525 were duplicates and 561 only contained meeting abstracts, 2551 articles were excluded

on the basis of title and 284 articles on the basis of abstracts. Two hundred articles were screened full-text. Seven articles were additionally excluded due to multiple or overlapping publications for the same population (the most recent or largest cohort publication remained). In the end, 32 articles were included. Two articles reported multiple studies and one article was added by hand-search (Figure 1). In total 33 articles, investigating 35 studies, were selected for the present review. Only one study reported the results of nested case control studies.

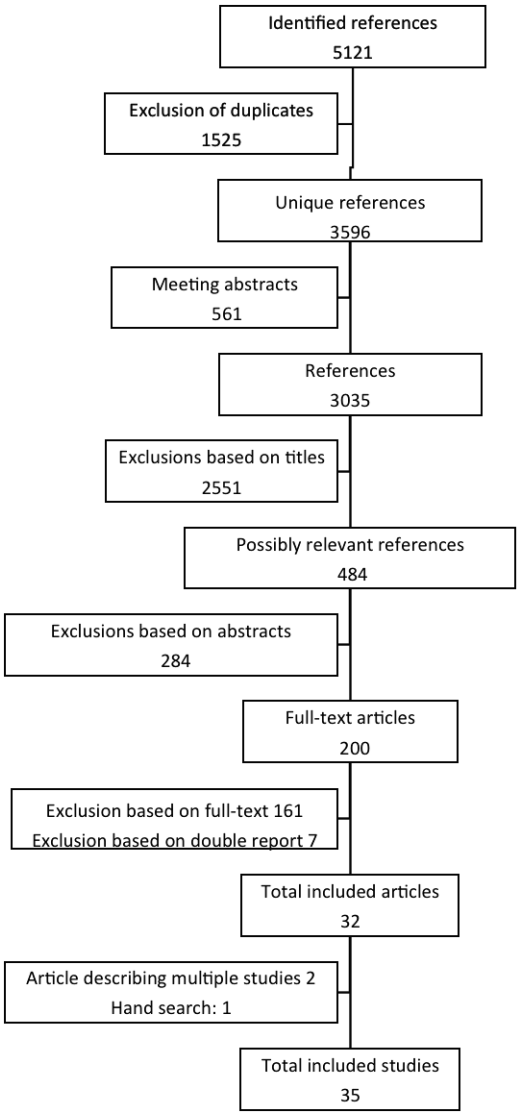

Figure 1. Flow chart of systematic review

Characteristics of included studies

Table 1 lists the characteristics of all OA studies.

A total of 499103 participants were included in 35 studies [2,4,7,8,11-39]. Two studies only included female participants, while both men and women were included in the other reported studies.[12,23] In studies reporting average age of the participants the age averaged between 54.5 and 91.9 years. Follow-up time ranged between 1 year and 42 years.

Most studies focused on knee or/and hip OA (n=24). Only one study reported shoulder OA.[11] Comparisons were mostly made with the general population using information from the country's bureau of statistics. One study used different radiographic scoring systems to define OA, while all other studies only used the Kellgren/Lawrence (K/L) score. Studies were conducted in one of three settings: patients undergoing arthroplasty, patients seeking care for their OA and persons with OA in the general population.

Study quality assessment

There was only one nested case control study and this study was of good quality with a clear description of the study, valid OA definition, cases and controls drawn from the same source population, valid measurements of the outcome and adequate analysis and presentation of the results.[37]

Of the 34 included cohort studies, the mean quality assessment was 62% (median was 70%, range 10 - 90%)(Table 2). ACR criteria were never used to define OA, radiographic definitions were however used in seven studies. One study used radiographic definition for part of the study[23]. Seventeen studies investigated total joint arthroplasty due to OA. Selection bias could sometimes not be determined due to a lack of information about exclusion criteria. The majority of the studies adjusted for age and gender to calculate the effect of OA in mortality. Standardized mortality ratios (SMRs) or HR were not often reported.

Association between osteoarthritis and mortality

Sixteen joint arthroplasty articles reported mortality in 17 studies, receiving either total knee or hip arthroplasty (Table 3A).[8,11,13,16,21,22,25-27,30,31,33-36,38] One study investigated mortality after total shoulder arthroplasty. There were seven high quality studies and all reported equal or lower overall mortality rates for OA patients when compared to the general population. One study reported a lower SMR at follow-up time of less than 10 years and a higher SMR at follow-up time of 10 years or more.[8]

Six studies involved patients consulting either their general practitioner or a medical specialist (Table 3B);[7,15,29,32,39] three of these studies were of high quality. None of these high quality studies reported an association between OA and mortality.

Table 1. Study characteristics of included studies (in alphabetical order of first author name)

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Amundsen; 2016[11]	Shoulder arthroplasty OA; 2006-2012; 1799; 66.5 (10.9); 58.9	General population	1	Death register
Barbour, 2015[12]	Radiographic hip OA from population based cohort; 1986-1988; 635; 71.4 (5.1); 100	Participants without radiographic hip OA	16.1 (6.2)	Death register
Böhm, 2000[13]	TKA; 1972-1994; 208; 72 (range 46-87); 84	General population	6	Hospital patient records
Cacciatore, 2014[14]	OA from population based study; 1992; 698; 74.8 (6.5); 80.1	Participants without OA	12	Death register
Danielsson, 1970[15]	Radiographic knee OA from hospital records; 1950-1958; 3994; NR	General population	NR	NR
Garellick, 1998[16]	THA; 1985-1989; 242; 70 (range 41-85) and 71 (range 40-86); 70% and 64%#	General population	8 (range 6-10)	Death register
Haara, 2003[17]	Finger OA (K/L≥2) from population register, 1978-1980, 1670, age groups 30-75+, 62	Participants without finger OA KL≥2	15-17, 43632 person-years	Death register
Haara, 2004[18]	Thumb CMC OA (K/L≥2) from population register, 1978-1980, 409, age groups 30-75+, 73	Participants without thumb CMC OA KL≥2	Up to 17	Death register
Haugen, 2015[19]	Radiographic or symptomatic hand OA from 'original' population based cohort and 'offspring' cohort; 1990-1994 for original and 1991-1995 for offspring; 1348; radiographic 66.1 (7.6) and symptomatic 66.6 (7.1); radiographic 74.2 and symptomatic 74.2	Participants without hand OA	Up to 19	Death register
Holbrook, 1990[20]	Knee, back, hand or hip OA from population based study; 1973-1975; 104; 50-70+; 63	Participants without OA	Up to 15 years	Death register
Holmberg, 1992[21]	THA;1978-1982; 518; 67 (range 40-88); 62	General population	At 6	Death register
Karuppiah, 2008[22]	THA; 1987-2007; 58; 91.9 (range 90-95); 67	General population	3.4 (range 2.9-3.8)	Hospital records, care taker or family doctor.
Kluzek, 2016[23]	Radiographic and symptomatic knee and hand OA from population based study; 1988-1989; radiographic knee OA 64, symptomatic OA 57, radiographic hand OA 166, symptomatic OA 99; knee 58.7-59.6 (4.9-6.3) hand 59.3-60.0 (5.1-5.5); 100	Participants without knee OA, participants without hand OA	Till 23 (median 21.7)	Death register

Table 1. Study characteristics of included studies (in alphabetical order of first author name) (*Continued)*

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Lee, 2007[24]	OA from national veterans health administration, 2000; 25 231; 58.8; NR	Veterans without common comorbid conditions	5	The Beneficiary Identification and Records Locator System
Lie, 2000[25]	THA; 1987-1998; 26433; age groups 69 (range ≤59 -≥80); 68	General population	Median 5.2 (range 0-10.4)	Death register
Lindahl 2007[26]	THA; 1979 to 2000; 63582; aged 50-90; 57	General population	108 700 py males, 143 000 py females	NR
Lindberg, 1984[27]	THA; 1968-1981; 974; median age group 65-69 (range 30-89); 64	General urban population	Range 0-13	Death register
Liu. Q, 2015[28]	Symptomatic and radiographic knee OA; 2005; symptomatic 63, radiographic 181; symptomatic 62.2 (8.6), radiographic 61.6 (9.2); symptomatic 71.4 radiographic 65.2	Participants without symptomatic OA, participants without radiographic OA	8 years	Interviewing relatives and death register of the local community office
Liu. R, 2015[29]	Multiple OA; 2000-2003; 383; 60 (7.6); 82	General population	Median 9.9 (range 1.83-11.9)	Death register
Liu. R, 2015[29]	Hand, knee or hip OA; 2005-2009; 460; 61 (9.9); 88	General population	Median 3.9 (range 0.0-6.8)	Death register
Lizaur, 2015[30]	TKA; 1994- 2003; 1569; median 68.2 (40-86); 76.7	General population	10	Death register
Michet, 2016[31]	THA and TKA from a population based cohort; 1969-2008; THA 1611, TKA 1938; THA median 68 (range 15-97), TKA 69 (14-93); THA 58 TKA 63#	General white population	11.9 (7.4)	Death register
Monson, 1976[32]	Hospitalized for arthritis; 1930-1960; 617; at death aged 75.9 females and 74,8 males; 73	General white population	12-42, 27% lost to FU	Local death register
Nüesch, 2011[2]	Knee or hip OA from population based cohort; 1994-1995; 1163; aged 35->75; 57	General population	Up to 15	Death register
Ohzawa, 2001[33]	TKA; 1989-1996; 53; 68.4 (range 42-83); NR	General population	2-9	NR

Table 1. Study characteristics of included studies (in alphabetical order of first author name) (*Continued)*

Studies First author; year of publication	Study setting*; inclusion period; no. patients; mean age (years, SD); proportion females (%)	Control	Follow-up mean number of years (SD)	Assessment of mortality in cohort
Pedersen, 2011[34]	THA; 1995-2006; 44558; age range 10->80; 56	Random sample by Danish Civil Registration System matched by age/gender	Up to 12,7 yr. <5 yr n=94410, 5-10 yr n=64453, >10 n=19386	Death register
Robertsson, 2007[35]	TKA; 1980-2002; 57979; 71(range 25-96); 65%	General population	Up to 28 after surgery. 382 427 person years	Death register
Schrøder, 1998[36]	TKA; 1989-1990; 761; aged 23 ->75;73#	General population	Up to 5 postoperatively	Death register
Schrøder, 1998[36]	THA; 1989-1990; 326; 23 ->75; 73#	General population	Up to 5 postoperatively	Death register
Tsuboi, 2011[37]	Knee OA from health checkup screening; 1997-1999; 244; 68.5 (±5.5); 70	Patients without knee OA	10	NR
Turkiewicz, 2016[7]	Health-care visits with diagnostic code knee OA or hip OA; 1998-2012; knee OA 51939, hip OA 29442; knee OA 70 (11), hip OA 72 (10); knee OA 60, hip OA 58	General population seeking health care and general population	10.3 (range 0-16)	Death register
Veronese, 2016[4]	Hand, hip or knee OA from population based cohort; 1995-1997; 1858; 77.5 (7.9); 66.4	Participants without OA	4.4	Death register
Visuri 2010[38]	THA, two surgery techniques: MM: 1967-1973; 579; age range 20- ≥80; 66 MP:1973-1985; 1585; age range 20- ≥80; 61.	General population	20-38	Death register
Visuri 2016[8]	TKA; 1980-1996; 9443; age 30-≥80; 79	General population	14	Death register
Watson, 2003[39]	UK General Practice Research Database; 163274; 54.5 (13.7) in men and 57.2 (15.1) in women; 62#	Patients with neither RA nor OA	Mean 4.7 males and 4.8 females.	Death was assessed by a code of deceased in the patient status field of the patient record, not verified by death records.

*Only data on OA group shown, unless unavailable
#study characteristics were only available for the entire study, which also included other diagnosis than OA.
SD=standard deviation;OA=osteoarthritis;TKA=total knee arthroplasty;NR=not reported;THA=total hip arthroplasty;K/L=Kellgren/Lawrence;CMC=carbometa carpal;MM=metal-on-metal;MP=metal-on-polyethylene

Table 2. Results of quality assessment scores in the cohort studies investigating mortality in osteoarthritis.

Study	Definition of study characteristics	Valid osteoarthritis definition	Description of subjects selection	Participation rate	Valid mortality measures	Valid mortality rates in controls	Frequencies of determinants	Frequencies of deaths	Appropriate analysis techniques	Adjusted for age and gender	Quality score
Amundsen[11]	1	0	1	1	1	1	0	1	1	1	80%
Barbour[12]	1	1	1	1	1	1	1	1	0	1	90%
Böhm[13]	1	0	0	1	0	1	0	1	1	1	60%
Cacciatore[14]	1	0	0	1	1	1	1	1	0	1	70%
Danielsson[15]	0	0	1	0	0	1	0	0	0	0	20%
Garellick[16]	0	0	0	1	1	1	0	1	1	1	60%
Haara 03[17]	1	1	0	1	1	1	1	1	0	1	80%
Haara 04[18]	1	1	0	1	1	1	1	0	0	1	70%
Haugen[19]	1	1	1	1	1	1	1	1	0	1	90%
Holbrook[20]	0	0	0	1	1	1	0	0	0	1	40%
Holmberg[21]	1	0	1	1	1	1	0	1	0	1	70%
Karuppiah[22]	1	0	1	1	0	1	0	1	0	0	50%
Kluzek[23]	1	0	1	1	1	1	1	1	0	1	80%
Kumar[40]	0	0	1	1	1	1	0	1	1	0	60%
Lee[24]	0	0	1	1	0	0	0	1	0	0	30%
Lie[25]	1	0	0	1	1	1	0	1	1	1	70%
Lindahl[26]	0	0	0	0	0	0	0	1	0	1	20%
Lindberg[27]	1	0	0	0	1	1	0	1	1	1	60%
Liu.Q[28]	1	1	1	1	1	1	1	1	0	1	80%
Liu.R GARP[29]	1	0	1	1	1	1	1	1	1	1	90%
Liu.R OCC[29]	1	0	0	1	1	1	1	1	1	1	80%
Lizaur[30]	1	0	1	1	1	1	1	1	1	1	90%
Michet[31]	0	0	0	1	1	1	0	1	1	0	50%
Monson[32]	0	0	1	0	1	1	0	1	1	1	60%
Nüesch[2]	1	0	1	1	1	1	1	1	1	1	90%
Ohzawa[33]	0	0	0	1	0	1	0	1	1	1	50%
Pedersen[34]	1	0	0	0	1	1	0	1	0	1	50%
Robertsson[35]	1	0	0	1	1	1	0	1	1	1	70%
Schrøder TKA[36]	0	0	0	0	1	1	0	1	1	1	50%
Schrøder THA[36]	0	0	0	0	1	1	0	0	0	1	30%
Turkiewicz[7]	1	0	1	1	1	1	0	1	0	1	70%
Veronese[4]	1	0	1	1	1	0	1	1	0	1	70%
Visuri[38]	1	0	0	1	1	1	0	1	1	1	70%
Visuri 2015[8]	1	0	0	1	1	1	0	1	1	1	70%
Watson[39]	0	0	0	0	0	0	0	0	0	1	10%

Table 3A. Results of studies investigating mortality in joint arthroplasty for osteoarthritis

First author [ref]	Mortality	Confounders adjusted for in the analyses
Amundsen[11]	Incidence rate: OA 945/100.000 and general population 1526/100 000	Age, sex
Böhm[13]	SMR: ♂1.14 (0.68-1.80), ♀1.03 (0.76-1.37)	Age, sex
Garellick[16]	Number of deaths in ♂: expected 31.4, observed 25 Number of deaths in ♀: expected 49.2, observed 34	Age, sex
Holmberg[21]	Number of deaths: OA n=83,15% (p<0.001) of expected mortality rate for general population	Age, sex
Karuppiah[22]	Survival times: longer in THA group than age matched general population (p<0.001); mean survival time: THA 96.13 (95%CI 95.35-96.91) and general population 93.72 (95%CI 93.65-93.79)	Age
Lie[25]	SMR: 0.68 (0.66-0.70)	Age, sex
Lindahl [26]	Death hazard: after a year equal to general population for age 60 and below. Higher age group: risk lower.	Age, sex
Lindberg[27]	Death observed/expected: >1 year since operation age 50-69 years ♀ 8/9.40, ♂ 13/16.06; age >70years ♀ 52/69.09, ♂ 45/46.55	Age, sex
Lizaur[30]	SMR: ♀ 0.779 (0.681-0.894), ♂ 0.928 (0.874-1.016)	Age, sex
Michet[31]	SMR: THA 0.81 (0.76-0.87) SMR: TKA 0.77 (0.72-0.83)	Age, sex
Ohzawa[33]	SMR: 0.11 (0.02-0.40)	Age, sex
Pedersen[34]	Mortality rates: THR vs general population.♀: 8.5 vs 11.7, ♂10.1 vs 13.5. Age 10-59 years 2.3 vs 2.4, 60-69 years 5.0 vs 6.8, 70-79 years 11.8 vs 16.1, >80 22.8 vs 35.9. Mortality rate ratios: calculated with adjust gender, age and Charlson comorbidity index. ♀ and ♂ 0.7 (0.7-0.7)	Age, sex, Charlson comorbidity index
Robertsson[35]	SMR: 0.77 (0.76-0.78.	Age, sex
Schrøder TKA[36]	SMR: 1 year FU 0.74 (0.60-0.87) Cumulative 5 year survival: 89%. No postoperative excess mortality	Age, sex
Schrøder THA[36]	Cumulative 5 year survival: 89%. No postoperative excess mortality	Age, sex
Visuri[38]	SMR: MM 0.96 (0.78-1.18) SMR: MP 0.90 (0.66-0.87)	Age, sex
Visuri 2015[8]	SMR: 1.00 (0.98-1.02)	Age, sex

OA=osteoarthritis; SMR=standardized mortality ratios (95% confidence intervals (CI)); THA=total hip arthroplasty; TKA=total knee arthroplasty; FU=follow-up; MM=metal-on-metal; MP=metal-on-polyethylene

Table 3B. Results of studies investigating mortality in osteoarthritis patients seeking health care

First author [ref]	Mortality	Confounders adjusted for in the analyses
Danielsson[15]	Expected death rates: higher in practically all age groups	Age
Liu GARP[29]	SMR: 0.54 (0.37-0.79)	Age, sex
Liu OCC[29]	SMR: 0.45 (0.25-0.82)	Age, sex
Monson[32]	SMR: 1.11	Age, sex
Turkiewicz[7]	HR knee OA: 0.92 (0.90-0.94) HR hip OA: 0.95 (0.93-0.97)	Age, sex, baseline confounders (income, highest level of achieved education, marital status, residential area and year of first health-care visit), comorbidities (ischemic heart diseases, cerebrovascular disease, diabetes mellitus, other malignant neoplasms, chronic obstructive pulmonary disease and malignant neoplasm of bronchus and lung
Watson[39]	SMR ♂: OA/no arthritis 19.5/20.6. ♀: OA/no arthritis 15.9/17.3.	Age, sex

GARP=Genetics ARthrosis and Progression;OCC=osteoarthritis care clinic;SMR=standardized mortality ratios(95% confidence intervals (CI));HR=hazard ratio(95% CI);OA=osteoarthritis

Table 3C. Results of studies investigating mortality in population based osteoarthritis

First author [ref]	Mortality	Confounders adjusted for in the analyses
Barbour[12]	HR: Croft grade ≥2 1.14 (1.05-1.24) HR: K/L grade ≥2 1.10 (0.99-1.22) HR: Croft grade ≥2 excluding THA 1.24 (1.13-1.35)	Age, BMI, education, smoking, health status, diabetes and stroke
Cacciatore[14]	HR: 1.28 (0.98-1.39)	Age, sex, BMI, waist circumference, heart rate, pulse blood pressure, Charlson co-morbidity index, number of drugs, NSAIDs, corticosteroids and geriatric depression scale
Haara 03[17]	RR: OA in any finger joint ♀ 1.17 (0.87-1.56), ♂ 1.02 (0.83-1.27) RR: Symmetrical DIP OA ♀ 1.23(1.01-1.51), ♂ 0.89 (0.68-1.16)	Age, education, history of workload, smoking and BMI
Haara 04[18]	RR: thumb CMC OA KL 2,3,4 no association RR: thumb CMC OA KL 3 or 4 ♀ no association ♂1.32 (1.03-1.69)	Age, sex and other unreported confounders

Table 3C. Results of studies investigating mortality in population based osteoarthritis *(Continued)*

First author [ref]	Mortality	Confounders adjusted for in the analyses
Haugen[19]	HR: Radiographic hand OA 0.82 (0.63-1.07) HR: Symptomatic hand OA 0.79 (0.57-1.10)	Age, sex, cohort, BMI, total cholesterol: HDL ratio, current lipid lowering treatment, increased blood pressure, current anti-hypertensive treatment, elevated fasting or non-fasting blood glucose, current antidiabetic treatment, previous cardiovascular events, previous cancer, current use of NSAIDs, daily use of aspirin, current/previous smoking, alcohol use.
Holbrook[20]	RR: ♀ 0.9, ♂ 0.8 For specific OA sites, mortality is not increased	Age, sex
Kluzek[23]	HR: Radiographic knee OA 1.05 (0.58-1.88) HR: Symptomatic knee OA 1.97 (1.20-3.22) HR: Radiographic hand OA, 0.91 (0.60-1.39) HR: Symptomatic hand OA 1.05 (0.66-1.66)	Age, smoking total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medication, occupation, BMI, hormone replacement therapy, past physical activity, current/previous CVD disease, non-ASA NSAIDs and glucose levels
Lee[24]	RR: 0.62 (0.58-0.67)	Age
Liu, Q[28]	HR: symptomatic knee OA: 1.9 (1.0-3.5) HR: radiographic knee OA: 1.2 (0.7-1.9)	Age, sex, BMI, income level, education, levels of occupational physical activity and comorbidities
Nüesch[2]	SMR: 1.55 (1.41-1.70)	Age, sex
Tsuboi [37]	Deaths after 10 years: OR 2.316 (1.412-3.801)	Age, sex, BMI and lifestyle
Veronese[4]	HR: All OA 0.95 (0.77-1.15) HR: Hand OA 1.00 (0.78-1.29) HR: Hip OA 0.96 (0.77-1.20) HR: Knee OA 0.86 (0.66-1.12)	Age, sex, BMI, educational level, alcohol drinking, monthly income, physical activity, presence at baseline of cardiovascular diseases, fractures, chronic obstructive pulmonary disease, orthostatic hypotension, hypertension, diabetes, frailty and cancer, number of medication smoking status, activities of daily living, mini-mental state, geriatric depression scale and geriatric nutrition risk index scores.

HR=hazard ratio (95% confidence intervals (CI)); K/L=Kellgren/Lawrence; THA=total hip arthroplasty; BMI=body mass index; NSAIDs=non-steroidal anti-inflammatory drugs; RR=relative risk (95% CI); OA=osteoarthritis; DIP=distal interhalangeal joint; CMC=carbometacarpal; HDL=high density lipoprotein; CVD non-ASA=non-acetylsalicylic acid; SMR=standardized mortality ratios (95% CI); OR=odds ratio (95% CI)

Twelve studies were based in the general population, of which ten were high quality studies (Table 3C).[2,4,12,14,17-20,23,24,28,37] Some studies reported separate results for more than one subtype of OA.[2,4,12,14,17-20,23,24,28,37] A meta-analysis was performed of the high quality studies based in the general population.

Four studies were excluded from the meta-analysis because of lack of outcome that could be summarized. Two of the excluded studies reported an association between mortality,[2,37] while two studies did not (Figure 2).[17,18] A meta-analysis of six studies (n=5169) resulted in a pooled HR of 1.04 (0.91-1.18).
Radiographic and symptomatic OA were also not associated with mortality when analyzed separately (data not shown).

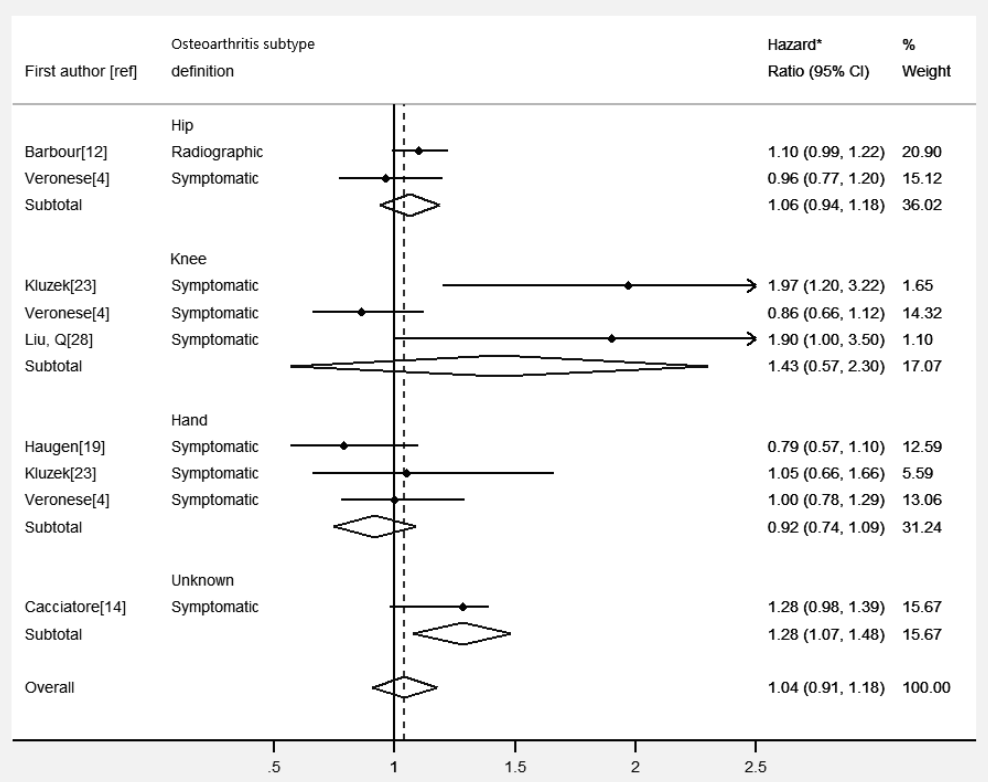

Figure 2. Meta-analysis

DISCUSSION

Overall we did not identify an association between OA and mortality when analyzing almost half a million patients. We explored whether patients with OA who presented themselves in a specific clinical setting could have an increased mortality risk that warrants attention. We investigated three clinical settings: OA patients receiving an arthroplasty, patients seeking care for their OA and OA in persons from the general population. All high quality studies which investigated

mortality in patients receiving a joint replacement for OA and in patients who sought help for their OA reported an equal or lower mortality rate for OA. However, the results from high quality population based studies were more diverse.

Two meta-analyses were performed previously and both studies found that OA was not significantly associated with mortality.[4,5] For the high quality studies investigating patients who received a joint arthroplasty and patients who consulted general practitioner or a medical specialist, no meta-analysis was done due to the heterogeneous outcomes used in the studies. These studies also had similar results and reported either equal or lower mortality rate. The meta-analysis summarizing 6 high quality studies investigating OA in persons from the general population also did not show an association of OA with mortality. In the latter meta-analysis four high quality studies were excluded due to a lack of similar outcomes. However, since two studies reported an increased risk and two studies did not, the influence of this exclusion on the overall pooled mortality rate is likely very limited.

One study [8] suggested that a follow-up time of 10 years or more may lead to a higher mortality rate in OA. This 'healthy cohort' effects may occur due to exclusion of patients with shortened life span. A 'healthy cohort' effect could also be present in studies including patients that have received a joint arthroplasty. Since this effect ebbs away after a couple of years, one article tested this hypothesis by delaying the start of follow-up.[29] However, mortality for OA patients did not increase. In the studies including patients that received a joint arthroplasty follow-up time differed, but especially in the high quality studies this was relatively long, making the 'healthy cohort' effect less likely. The absence of a 'healthy cohort' is further supported by several studies with longer follow up time, which also did not find an increased risk for mortality.[19,38]

Another possible explanation may be that patients seeking care for their OA and receiving a knee or hip arthroplasty are also patients who in general take better care of themselves or possess a better general health. Population studies also include patients who are less in tune with their health. However, in the study by Turkiewicz et al, additional analyses were done using patients without OA who sought care as a control group.[7] These analyses did not change the lack of association between OA and mortality. So, this aspect cannot explain the total difference.

OA subtypes were not equally investigated. The majority of the studies included knee or hip OA patients while only five studies reported mortality for hand OA.

Some studies did not specify the subtype of OA or combined subtypes and could thus offer no additional insights into the influence of the individual subtype. Though not significant, higher rates of mortality were more often reported for patients with knee OA. It is possible that the association between OA and

mortality may depend upon the OA subtype, possibly in combination with potential confounders. However, since these confounders were not equally investigated in previous studies, too little evidence is currently available to conclude the influence of the OA subtype on mortality.

The majority of the analyses were performed using only age and sex as confounding factors and the general population as controls. One study[23] reported different results when different combinations of additional confounders were used, while another study found similar results. As too few studies were performed using different sets of additional confounders, it is possible that some additional confounders than age and sex should be used. However, this would only be statistically feasible if large cohorts with long follow-up time were used.
The presence of publication bias cannot be ruled out. It is possible that negative associations between OA and mortality have been underreported. A few smaller sized studies in knee or hip OA reported an association between OA and mortality, while a large study in which more confounders were used found no association.
The results of this systematic review suggest that OA is not associated with mortality in patients receiving knee or hip arthroplasty or seeking care. Mortality associated with OA in persons in the general population was not increased, however these studies were equivocal and results may depend on the OA subtype and potential confounders. More well conducted and large studies with long follow-up periods will be necessary to analyze the association between OA and mortality.

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APPENDICES (ONLINE SUPPLEMENTAL FILES)

Appendix I. Overview of search strategy and results

	Key Words	Number of Articles
PubMed	"Osteoarthritis/mortality"[Mesh] OR (("osteoarthritis"[Majr] OR Osteoarthrosis[ti] OR Osteoarthroses[ti] OR Osteoarthritides[ti] OR Osteoarthritis[ti] OR Osteoartrosis[ti] OR Osteoartroses[ti] OR Osteoartritides[ti] OR Osteoartritis[ti] OR "Degenerative Arthritis"[ti] OR "Degenerative Arthritides"[ti] OR Arthrosis[ti] OR Arthroses[ti] OR Arthritides[ti] OR Artrosis[ti] OR Artroses[ti]) AND (Mortality OR "Mortality"[mesh] OR "mortality"[Subheading] OR Mortality[tw] OR Mortalities[tw] OR "Case Fatality Rate"[tw] OR "Case Fatality Rates"[tw] OR "Death Rate"[tw] OR "Death Rates"[tw] OR "Cause of Death"[tw] OR "Fatal Outcome"[tw] OR "Fatal Outcomes"[tw] OR "Survival Rate"[tw] OR "Survival Rates"[tw] OR "Death"[mesh] OR "Survival"[mesh] OR "Survival Analysis"[mesh] OR survivorship[tw])) OR (("osteoarthritis"[Mesh] OR Osteoarthrosis[tw] OR Osteoarthroses[tw] OR Osteoarthritides[tw] OR Osteoarthritis[tw] OR Osteoartrosis[tw] OR Osteoartroses[tw] OR Osteoartritides[tw] OR Osteoartritis[tw] OR "Degenerative Arthritis"[tw] OR "Degenerative Arthritides"[tw] OR Arthrosis[tw] OR Arthroses[tw] OR Arthritides[tw] OR Artrosis[tw] OR Artroses[tw]) AND ("Mortality"[majr] OR "mortality"[Subheading] OR Mortality[ti] OR Mortalities[ti] OR "Case Fatality Rate"[ti] OR "Case Fatality Rates"[ti] OR "Death Rate"[ti] OR "Death Rates"[ti] OR "Cause of Death"[ti] OR "Fatal Outcome"[ti] OR "Fatal Outcomes"[ti] OR "Survival Rate"[ti] OR "Survival Rates"[ti] OR "Death"[majr] OR "Survival"[majr] OR "Survival Analysis"[majr] OR survivorship[ti]))	1541
Embase	((exp *osteoarthritis/ OR (Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses).ti) AND (exp mortality/ OR exp Death/ OR exp survival rate/ OR (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship).ti,ab)) OR ((exp osteoarthritis/ OR (Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses).ti,ab) AND (exp *mortality/ OR exp *Death/ OR exp *survival rate/ OR (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship).ti))	2452
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	180

Appendix I. Overview of search strategy and results *(Continued)*

	Key Words	Number of Articles
Web of Science	(TI=(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND TS=(Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)) OR (TS=(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND TI=(Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship))	546
	TITLE-ABSTR-KEY(Osteoarthritis AND Mortality)	154
	TITLE-ABSTR-KEY((Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR Degenerative Arthritis OR Degenerative Arthritides OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR Case Fatality Rate OR Case Fatality Rates OR Death Rate OR Death Rates OR Cause of Death OR Fatal Outcome OR Fatal Outcomes OR Survival Rate OR Survival Rates OR Survival Analysis OR survivorship))	
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR Degenerative Arthritis OR Degenerative Arthritides OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR Case Fatality Rate OR Case Fatality Rates OR Death Rate OR Death Rates OR Cause of Death OR Fatal Outcome OR Fatal Outcomes OR Survival Rate OR Survival Rates OR Survival Analysis OR survivorship)	
	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	

Appendix I. Overview of search strategy and results *(Continued)*

	Key Words	**Number of Articles**
CINAHL	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	228
Academic Search Premier	(Osteoarthrosis OR Osteoarthroses OR Osteoarthritides OR Osteoarthritis OR Osteoartrosis OR Osteoartroses OR Osteoartritides OR Osteoartritis OR "Degenerative Arthritis" OR "Degenerative Arthritides" OR Arthrosis OR Arthroses OR Arthritides OR Artrosis OR Artroses) AND (Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "Cause of Death" OR "Fatal Outcome" OR "Fatal Outcomes" OR "Survival Rate" OR "Survival Rates" OR "Survival Analysis" OR survivorship)	20
Hand Search		1

Appendix II

Item	Criteria	Applicable for:
1	Definition of study Sufficient description of characteristics of study groups *A '1' is given when a paper describes at least setting and time of period of the study, ages of patients (and its range) and man:woman ratio*	C/NCC
2	Presence of OA was according to valid definition and the classification was standardized. *A '1' will than given for a study which used ACR criteria for OA or a valid OA radiographic scoring method (such as Kellgren and Lawrence, OARSI or Croft)*	C/NCC
3	Presence of OA was measured identically in cases and controls. *A '1' is given if assessment of mortality was the same in controls as in cases.*	NCC
	Selection bias	
4	Clear description of selection of study subjects. When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.	C/NCC
5	Cases and controls were drawn from the same source population. This is to exclude the possibility of selection bias.	NCC
	Follow-up	
6	Participation rate ≥ 80% for study groups	C/NCC
7	80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.	NCC
8	No difference in withdrawal in both groups, including information on completers and withdrawals	C/NCC
	Assessment of the outcome: Death	
9	Mortality measures were valid, e.g. the use of national register or objective observations	C
10	Valid mortality rates in controls *A '1' is given if mortality rates in controls are valid, e.g. country life tables or register*	NCC
11	Mortality was assessed identical in cases and controls A '1' is given if assessment of mortality was the same in controls as in cases.	C/NCC
	Analysis and Data Presentation	
12	Frequencies of the most important determinants were given, such as age, BMI, sex	C/NCC
13	Frequencies of deaths were given Appropriate analysis techniques with estimates were used *A '1' is given if SMRs are calculated or may be calculated from observed/ expected*	C/NCC
14	Adjusted for at least age and gender	C/NCC