HHS Public Access

Author manuscript

Clin Exp Rheumatol. Author manuscript; available in PMC 2019 December 27.

Published in final edited form as:

Clin Exp Rheumatol. 2019 ; 37(Suppl 120): 24–30.

Knee and hip osteoarthritis as predictors of premature death: a review of the evidence

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Abstract

Rheumatic and musculoskeletal diseases (RMDs) are common, with osteoarthritis (OA) being the most prevalent. RMDs, including OA, are associated with significant pain and functional limitations, as well as mortality rates up to 1.6-fold higher than in the general population. Most studies of OA and mortality have focused on knee and hip OA. Some, but not all, of these studies suggest an increased risk of death, however risks may differ by region. Reasons for discordant findings may be due to methodological considerations including definition of OA, study design, length of follow-up, and whether variables that can change and develop over time, such as measures of OA, body mass index (BMI) and comorbidities, were re-assessed during the follow-up period. Research has shown that the prognosis of OA is similar to that seen in rheumatoid arthritis (RA) patients, in many respects. In RA, disability and comorbidities are the most important predictors of mortality, although pain may be more prominent in the prognosis of OA mortality. The data suggest that addressing functional limitations and pain seen with OA could potentially reduce the increased mortality that has been observed in these individuals. Further study is needed concerning the potential excess mortality attributable to lower body OA, as well as associated disability, pain and comorbidities.

Keywords

osteoarthritis; hip OA; knee OA; mortality; premature mortality

Introduction

Rheumatic and musculoskeletal diseases (RMDs) are highly prevalent and associated with significant pain, disability, and also increased levels of mortality (1, 2). In the 1940s scientists began to study the causes of death in rheumatoid arthritis (RA) patients (3) and it has been shown that mortality rates in RA patients are up to 1.6-fold higher than in the

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Competing interests:
A.E. Nelson has declared no competing interests.

general population (4). Further, in an early review most rheumatic diseases were noted as having a role in premature death including RA, ankylosing spondylitis, systemic lupus erythematosus, vasculitis (5). However, the effects of osteoarthritis (OA) on mortality were largely ignored until the past few decades.

A review of mortality in OA published in 2008 concluded that there was moderate evidence of increased risk of mortality in individuals with OA (6). Since that time, a number of further investigations have examined whether OA is associated with excess mortality. Some studies have reported on hand (7–9), spine (10) or non-specific joint OA (9, 11, 12) and have generally reported null results. Yet many studies have reported that elevated risks of death are seen in OA of the hip (11, 13) and/or knee (8, 10, 14, 15). Knee and hip OA are common and are associated with significant pain and functional limitations (16). Lower body OA is a leading cause of disability and has also been shown to be a main contributor to loss of quality adjusted life-years (17). In a 2014 report of the global burden of knee and hip OA, these conditions were ranked eleventh on the list of contributors to global disability (18).

It has been suggested that observed associations between OA and excess mortality could be due primarily to disability since pain and functional limitations are independently associated with mortality (19), or that the effect of OA on mortality is mediated through walking disability and/or use of non-steroidal anti-inflammatory drugs (NSAIDs) (Fig. 1) (20). This idea was supported by Hawker and colleagues who reported that among those with OA, individuals with higher levels of disability also had greater risk for serious cardiovascular disease (CVD) events and all-cause mortality (21). With the rise in obesity and our aging society, the burden of OA with its accompanying disability and comorbid conditions will lead to an expected increase in premature deaths. Therefore, it is important to understand and continue to study the potential excess mortality attributable to lower body OA as well as its associated disability, pain and comorbidities.

Summary of knee and hip OA mortality studies

As noted above, until a systematic review of 8 studies conducted to date was published in 2008, little attention was paid to the contribution of OA to mortality (6). This review reported that there was moderate evidence that OA leads to increased risk of death. Several studies have investigated mortality associated with OA over the past 10 years, most examining the effects of knee and/or hip OA which will be the focus of this review.

Knee OA studies—Some studies that have focused on knee OA have found reduced or no associations with all-cause mortality (9, 11, 22, 23), while others have reported modest associations (14, 24), or increases in mortality for those with OA among Asian populations (10, 15) and those with painful knee OA (8, 14, 15) (Table I). Results from two traditional meta-analyses found non-significant increases in risk of death from knee OA (hazards ratio [HR]=1.21, 95% confidence interval [CI]=0.83–1.78 and HR=1.24, 95% CI=0.87–1.76) (9, 25). Although traditional meta-analyses are valuable and efficient, they are limited to published data and may suffer from publication biases. To try to overcome some of the possible limitations in the meta-analyses, an individual patient data (IPD) meta-analysis using standardised statistical methods and definitions of exposures, confounders and

outcomes, as well as original raw data from several international cohorts was conducted (26). The IPD results showed that risk of death due to symptomatic knee OA (defined as having both OA and pain in the same joint) differed according to whether the study was carried out in the United States (US) or some-where else in the world, noting higher risk in US populations (HR US=1.23, 95% CI=1.07–1.42 *vs.* HR rest-of-world=0.72, 95% CI=0.39–1.35) (26). The differences seen between US and other populations may be due to many factors including increased obesity, disability, comorbidities, access to healthcare and low levels of physical activity in the US population (27).

Hip OA studies—Fewer studies have reported on the probable association between hip OA specifically and death (9, 11, 13, 23). Of these, most have reported no inported creased risk of all-cause death with hip OA (9, 11, 23). Results from traditional meta-analyses also have found no increased risk of death for hip OA (9, 25). However, one study in a cohort of older women in the US reported a 10% increase in all-cause mortality that approached statistical significance (HR=1.10, 95% CI=0.99–1.22) (13) (Table II). Further, results from the IPD meta-analysis of US cohorts for the association of hip pain on mortality found increased risks, with a pooled HR=1.20 (95% CI=1.04–1.37) (26).

Disease-specific mortality—Of the studies that have assessed the association between knee and/or hip OA and mortality, only a few have reported on disease-specific causes of death. Of those studies, the most commonly reported cause of death is due to CVD. Cardiovascular disease has been closely linked to OA and is thought to be one of the major causes of morbidity among those with OA, with previous reports showing increased CVD in those with OA (21, 28–30). Further, a study of individuals with OA showed increased deaths due to CVD (31). In all studies that assessed both all-cause and CVD-specific mortality, estimates of the effect of lower body OA were stronger for CVD-specific mortality than for all-cause mortality (8, 10, 13, 14, 24). One study of older women reported increased risk of CVD-specific death in those with hip OA (HR=1.24, 95% CI=1.13–1.35) (13). Another recent study that only assessed cause-specific death reported increased risks for CVD-specific mortality for both knee and hip OA (HR=1.16, 95% CI=1.07–1.26; and HR=1.13, 95% CI=1.03–1.25, respectively) (32). Further, these associations with CVD-specific mortality seem to be particularly strong for those with painful knee radiographic OA (rOA) when compared to those with neither rOA nor pain, with hazards ratios ranging from 1.32 to 3.57 (8, 14).

Summary—There is a trend of most studies showing an increased risk of death for knee and hip OA particularly in US populations: however, some studies have shown no association or a decreased association. Further, many traditional meta-analyses that pooled estimates from both US and rest-of-world cohorts tended to report no association between OA and premature death, whereas the IPD analyses which used original raw data and separated the US and other regions reported increased mortality risks in US cohorts. This may be due to many factors including increased obesity, disability, comorbidities, access to healthcare and low levels of physical activity in the US population (27).

Methodologic considerations

While some studies have provided evidence that knee and/or hip OA may lead to increased risk of death, others have reported null findings (9, 11, 23, 33). Possible reasons for these discordant findings are potentially due to how OA was defined in the study, study design, length of follow-up, and whether variables that can change and develop over time such as measures of OA, body mass index (BMI) and comorbidities were re-assessed during the follow-up period.

Definition of OA—In studies using physician clinically diagnosed OA, in which comorbidities and disability were taken into account in analyses, the association between OA and mortality was often greatly attenuated or no longer remained (11, 33). However, the estimates of mortality in some studies using radiographically confirmed OA (rOA) seem to be less affected by adjusting for disability and comorbidities in those analyses (8, 14). There are several possible reasons for this. First, studies that use physician clinical diagnosis as their measure of OA are selecting individuals who are already experiencing joint pain and seeking care for it, whereas those who do not consult a physician tend to have less pain (34). Thus, those with painful joints are the ones who will be diagnosed with OA in a clinical or registry-based study. It is also possible that radiographic OA alone may be a weaker predictor of mortality since it has been shown that rOA does not always predict pain and therefore may not be as affected by adjustment for disability (35). We know that pain is one of the major barriers to exercise which can lead to increased comorbidities and subsequent disability. It has also been suggested that pain may be the main driver of the excess in mortality seen with OA, an association which has been reported in several studies (36–38). Studies using symptomatic knee rOA (rOA and pain in the same joint) as a distinct predictor of mortality seem to support this. Two studies reporting on four mutually exclusive groups of no knee OA, radiographic knee OA (rOA) only, knee pain only or symptomatic knee rOA both reported the highest HRs in the symptomatic knee rOA group (8, 14). One of these, a population-based cohort with over 4,000 participants followed over 24 years, showed that those who have symptomatic knee rOA had the worst survival followed closely by those with knee pain alone (Fig. 2) (14). Conversely, a recent report on the association of symptomatic knee OA on subsequent mortality using data from four international studies did not show any increased risk of death after adjustment for covariates, including comorbidities (33). However, as is common in studies using a physician clinical diagnosis of OA, the four studies included in that report did not provide details on how physicians made the diagnosis of OA and therefore the precise definition of OA was not clear in these studies. As a result, there likely was some misclassification of symptomatic knee OA in studies using a physician clinical diagnosis of OA. However, we know that the diagnosis of OA is often largely clinical and may be diagnosed based on presentation of pain, stiffness and swelling (39, 40), where radiographic findings do not always correlate with symptoms and are sometimes only used to rule out other diagnoses (41).

Another potential reason for the discordant findings is that since the participants in studies using physician clinically diagnosed OA data by definition have symptomatic OA, these studies lack a non-symptomatic rOA group as a comparison. Consequently, all comparisons are of those with symptoms compared to those without symptoms, regardless of whether a

patient has radiographic disease. This could lead to lower estimates of risk since joint pain alone has been shown to be a predictor of death (8, 14, 36, 37). These individuals will also likely have a higher level of disability since they are already in pain. Therefore, once disability and pain were adjusted for in these analyses, the effect of OA was greatly reduced.

On the other hand, studies using radiographically confirmed OA (rOA) included many individuals who did not necessarily have joint pain and/or accompanying disability. One study found that 47% of individuals with radiographic knee OA did not report having knee pain (35). This may suggest that studies assessing OA radiographically may be able to capture individuals with rOA before they experience pain and accompanying disability, potentially reflecting a true association with rOA that is independent of pain and disability. Conversely, in physician clinically diagnosed OA studies it is possible that there is an underlying association between rOA and mortality that is masked by disability and/or comorbidities that are included in analyses.

Follow-up time and repeated measurement of OA and covariates—When interpreting OA and mortality analyses, it is important to consider study design aspects that can affect the results including follow-up time and number/frequency of measurements assessing whether the individual has OA. Of particular concern with a chronic disease like OA is that there is the potential that the impact of OA on mortality may only manifest later in the disease course. Therefore, studies with a short follow-up time may be more prone to lower estimates of risk. On the other hand, studies with longer follow-up are subject to greater losses of participants over time which can be a problem in estimating outcomes. However, since the outcome in question is mortality, which in most studies was obtained through nationally linked databases, loss-to-follow-up in terms of the outcome is not as large an issue. In the case of mortality due to OA, there does not seem to be any consistent pattern of lower risk of mortality with shorter follow-up time in studies of either knee or hip OA.

Traditionally, most community-based mortality studies have examined OA from a static perspective; *i.e.* researchers examine how OA predicts mortality over the years that follow after the single initial assessment of OA status. Only two of these studies estimated the effect on mortality as OA status was assessed over time. Both of these studies found increases in all-cause mortality that narrowly missed statistical significance, and statistically significant increases in CVD deaths (13, 14). In studies using registry data it is unclear whether the OA measurements and comorbidities included in the analyses were assessed in a time-varying manner (*i.e.* assessed, reported and used in the analyses at multiple time points over the follow-up period).

Data sources—The choice of data source, whether a large registry, or one or more community-based cohorts, may influence the estimated associations. Using registry or claims data samples is convenient and provides the opportunity to capture other physician clinically diagnosed comorbidities. However, the composition of these samples is influenced by various factors that limit their generalisability, such as demographics, provider referrals and access to health care. Several of the registry data studies were conducted in countries with universal healthcare where seemingly all citizens have equal access. However, even in universal single-payer healthcare systems, utilisation of services is affected by

socioeconomic status (SES), where those with lower SES tend to visit general practitioners while those with higher SES visit more specialists and have more access to diagnostic imaging and specialised treatments (42). Conversely, community-based studies are better able to determine prevalence and incidence in the general population. While these types of studies can suffer from simplified or poor diagnosis methods for OA (*e.g.* self-report), all of the community-based studies of the effects of lower body OA on mortality used radiographically defined OA as their measure and therefore are not subject to the same measurement error (9, 10, 14, 15). In these circumstances, differences noted for estimates of the effect of OA on mortality found in community-based studies and compared with the estimates seen for the clinic samples may reflect differences in OA diagnosis or, more likely, differences in population sampling.

Discussion

It may be useful to further understand whether the higher risk of mortality is due to systemic effects of OA or the consequences of disability or limited physical activity. As noted above, it has been suggested that the underlying mechanism of OA on mortality is through pain, disability and/or NSAIDs (Fig. 1) (20). A recent study suggested that the increase in CVD-specific mortality is due to disability, not OA itself (32). Evidence presented for this was that only lower limb OA (knee and hip) showed increases in CVD mortality, while other joint sites such as the hand did not. This idea is supported by another study reporting that it is disability, not OA that predicts CVD itself (43).

OA researchers can take lessons learned from RA outcomes research. The research suggests that the prognosis of OA is similar in some ways to that seen in RA patients (44), which has shown that disability and comorbidities are the most important predictors of mortality in RA (4), although pain may also be important in the prognosis of OA mortality (8, 14). Recent studies suggest that the burden of disability and pain seen in RA patients is similar to that in OA patients (45, 46). So, while clinicians may view OA and RA as very different diseases in terms of management, they both confer a similar risk of disability, pain, comorbid conditions and mortality that should be considered similarly.

Our current options to prevent OA are limited, including maintaining a healthy body weight and avoidance of joint injury. Additionally, no disease-modifying drugs are available that affect structural changes in OA. However, these studies indicate that there is likely an important role for prevention of disability, particularly mobility disability, to reduce excess mortality in individuals with OA. This highlights the importance of weight reduction, physical activity and physical/occupational therapy in the management of OA, as these modalities are most likely to reduce disability (47–49). The role of pain management, which itself is a complex area, is also key, given the apparent associations between persistent painful lower body OA and excess mortality (50).

Conclusion

There is moderate evidence that knee OA is associated with premature mortality. There is also evidence that both knee and hip OA are associated with death in US populations. Much

of the research on excess mortality in OA focuses on disability as being the responsible factor, however OA is likely the cause of the majority of disability and therefore cannot be discounted as an underlying factor. Addressing the symptoms and functional limitations that lead to disability among those with knee or hip OA could potentially reduce the increased mortality rates that have been observed in these individuals.

Acknowledgments

Funding: support for this manuscript was provided in part by the Multidisciplinary Clinical Research Center (MCRC) of the UNC Thurston Arthritis Research Center, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) 5P60AR064166; NIAMS 1R01AR065937; and Centers for Disease Control and Prevention (CDC) U01DP006266.

R.J. Cleveland receives grant support from the NIH and CDC; L.F. Callahan receives grant support from the NIH, CDC and Pfizer, honoraria from the NIH for grant reviews, and has consulted for AbbVie in 2019;

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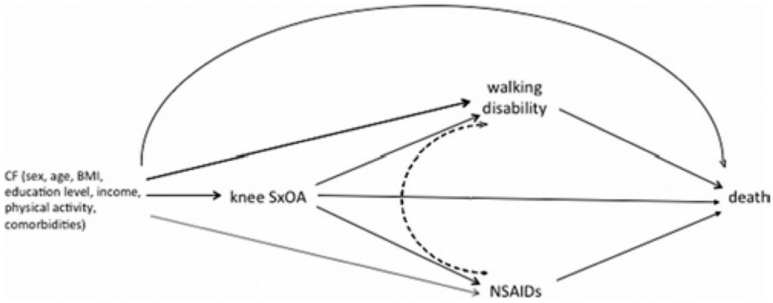

Fig. 1.

A directed acyclic graph to describe the hypotheses: we decomposed the total effect of knee symptomatic osteoarthritis (SxOA) on all-cause mortality into two components: 1) the indirect effect (or mediated effect), *i.e.* the effect of knee SxOA on all-cause mortality mediated through either a walking disability (knee SxOA→ walking disability → death) or Non-steroidal antiinflammatory drugs (NSAIDs) use (knee SxOA→ NSAIDs→ death), and 2) the direct effect, *i.e.* the effect of knee SxOA on all-cause mortality (knee SxOA→ death) that was not through either a walking disability or use of NSAIDs. The dotted line between walking disability and NSAIDs indicated that the time sequence was uncertain. CF: confounders.

Source: Liu Q, Niu J, Li H *et al.*: Knee symptomatic osteoarthritis, walking disability NSAIDs use and all-cause mortality: population-based Wuchuan Osteoarthritis Study. *Sci Rep* 2017: 7: 3309.

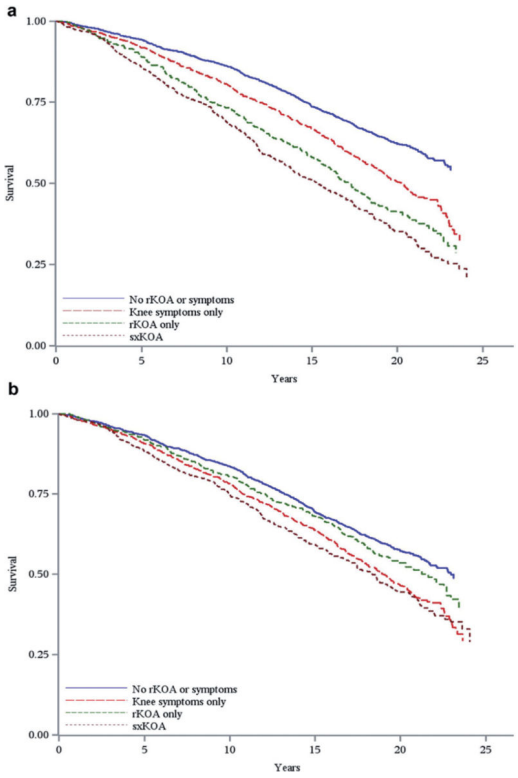

Fig. 2.

Kaplan-Meier survival curves for mortality by baseline knee rOA and/or knee pain group, unadjusted (**a**) and for age and sex (**b**).

Source: Cleveland RJ, Alvarez C, Schwartz T *et al.*: The impact of painful knee osteoarthritis on mortality: a community-based cohort study with over 24 years of follow-up. *Osteoarthritis Cartilage* 2019; 27: 593-602.

Table I.

Publications on knee OA and mortality.

Year	Author	Study period	Study population	Number of participants	Age of participants	Length of follow-up	All-cause mortality	Estimate of effect (HR or OR)	
								Men Overall	Women Overall
Radiographically confirmed knee OA									
2011	Tsuboi[10]	1997–2007	Rural community; Japanese men and women	789	>60	10-year follow-up	OR=2.32 (1.41–3.80)		
2015	Kluzek[8]	1993–2014	Women from a single practice in England; predominantly Caucasian	821	≥45	Median 21.7 years (range: 21.2–22.3)			OVERALL ref=no OA or pain HR OA only=1.05 (0.58–1.88) HR Pain only=1.44 (0.99–2.08) HR SxOA=1.97 (1.20–3.22)
2015	Liu Q[15]	2005–2013	Rural community; Chinese men and women	1025	≥50	8-year follow-up	HR SxOA=1.9 (1.0–3.5) HR rOA=2.2 (0.7–1.9)		
2016	Veronese[9]	1995–2001	Two communities-incl. nursing homes in Northern Italy; Caucasian men and women	2927	≥65	Mean 4.4 years	HR=0.86 (0.66–1.12)		
2018	Mendy[24]	1999–2011	Survey data from 1991–1996 NHANES with radiographs; Caucasian-African American and Mexican American men and women	2,589	≥60	Median 13.6 years (IQR: 7.4–18.2)	HR=1.06 (0.99–1.14) HR rOA=0.99 (0.90–1.09) HR SxOA=1.13 (1.01–1.26)		
2019	Cleveland[14]	1991–2015	Six rural communities in NC; Caucasian and African	4,182	≥45	Median 14.7 years (range: 0–24.6)	ref=no OA or pain HR OA only=0.95 (0.83–1.09) HR Pain only=1.18 (1.03–1.34) HR SxOA=1.17 (1.02–1.33)	OVERALL ref=no OA or pain HR OA only=0.87 (0.71–1.07) HR Pain only=1.04 (0.85–1.27) HR SxOA=1.13 (0.93–1.38)	OVERALL ref=no OA or pain HR OA only=1.03 (0.85–1.24) HR Pain only=1.30 (1.09–1.54) HR SxOA=1.22 (1.03–1.44)
Physician clinically diagnosed knee OA									

Year	Author	Study period	Study population	Number of participants	Age of participants	Length of follow-up	All-cause mortality	Estimate of effect (HR or OR)	
								Men Overall	Women Overall
2015	Liu R[11]	2000–2011	Sibling pairs with SxOA at multiple sites in the Netherlands; Caucasian men and women	383	>40	Median 9.9 years (range: 1.83–11.9)	HR=0.59 (0.25–1.41)		
2016	Turkiewicz[23]	1998–2012	Swedish registry data; Caucasian men and women	51,939	≥45	Mean 10.3 years (range: 0–16)	HR=0.87 (0.85–0.89)	0.89 (0.86–0.92)	0.85 (0.83–0.87)
2018	Mendy[24]	1988–2011	Survey data from NHANES and NCHS; Caucasian-African American and Mexican American men and women	51,938	≥20	Median 8.9 years (IQR: 4.6–17.6)	HR=0.96 (0.87–1.06)		
2019	Yang[33]	ELSA (2002–2012) SHARE (2004–2015) KLoSA (2006–2014) IFLS (2007–2015)	Survey cohorts; men and women of varying races from England, Europe, a Korea nd Indonesia	10,851 28,533 9,920 10,218	≥50 ≥50 ≥45 ≥40	10-year follow-up 11-year follow-up 8-year follow-up 8-year follow-up	HR SxOA=1.07 (0.94–1.20) HR SxOA=1.08 (0.97–1.22) HR SxOA=0.91 (0.77–1.08) HR SxOA=0.89 (0.66–1.21)		

OA: Osteoarthritis; rOA: radiographic OA; SxOA: symptomatic OA.

Table II.

Publications on hip OA and mortality.

Year	Author	Study period	Study population	Number of participants	Age of participants	Length of follow-up	Estimate of effect (HR or OR) All-cause mortality	Men Overall	Women Overall
Radiographically confirmed hip OA									
2015	Barbour[13]	1988–2013	Radiographic hip	7889	≥65	Mean 16.1 yrs (SD=6.2)			HR=1.10 (0.99–1.22)
2016	Veronese[9]	1995–2001	Two communities, incl. nursing homes in Northern Italy; Caucasian men and women	2927	≥65	Mean 4.4 years	HR=0.86 (0.66–1.12)		
Physician clinically diagnosed hip OA									
2015	Liu R[11]	2000–2011	Sibling pairs with SxOA at multiple sites in the Netherlands; Caucasian men and women	383	>40	Median 9.9 years HR=1.55 (0.70–3.45) (range: 1.83–11.9)	HR=1.55 (0.70–3.45)		
2016	Turkiewicz[23]	1998–2012	Swedish registry data; Caucasian men and women	51,939	≥45	Mean 10.3 years (range: 0–16)	HR=0.90 (0.87–0.92)	HR=0.90 (0.87–0.94)	HR=0.90 (0.86–0.93)

OA: Osteoarthritis; rOA: radiographic OA; SxOA: symptomatic OA.