Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration
December 1, 2016

Osteoarthritis: A serious disease

OVERVIEW

The importance of osteoarthritis

- ***Highly prevalent globally***
- ***Both prevalence and risk factors are increasing***
- ***No known cure***
- ***Significant impact in years life lost due to disability***
- ***Significant impact on and by comorbid conditions***
- ***Increased risk of dying prematurely***
- ***Loss of productivity; early retirement; loss of retirement savings***
- ***High economic burden to individuals and society***
- ***Natural history of progression with no known remission***
- ***No proven interventions yet available to stop the progression***
- ***Current therapies have small treatment effect, are costly and associated with life-threatening adverse effects***

EXECUTIVE SUMMARY

The global impact of osteoarthritis (OA) constitutes a major worldwide challenge for health systems in the twenty-first century. In 2005, 26.9 million US adults were estimated to have OA, up from 21 million in 1990.

OA accounts for 2.4% of all years lived with disability (YLD) and has been ranked as the 10th leading contributor to global YLDs. The global prevalence of hip and knee OA is approaching 5% and is projected to increase as the population ages. Obesity rates are also rising globally, and as obesity is a strong risk factor for knee OA and may also increase the rates of hip, hand and spinal OA, rates of these painful conditions, together with their associated disability and loss of function, will continue to increase.

The trends in OA YLDs from 1990 to 2013 showed a 75% increase, the third most rapidly rising condition associated with disability, just behind diabetes at 135% and dementia at 84%. The most recent update of the Global Burden of Disease figures, (GBD 2013) estimated that 242 million people were living in the world with symptomatic and activity limiting OA of the hip and/or knee, accounting for 13 million YLDs. These figures are likely to be an underestimate of the true global burden of OA, as these rates only consider hip and knee OA, and not OA at other sites.

The economic burden of arthritis on patients and society is high in every country that it has been estimated. In 2003 the total costs attributable to arthritis and other rheumatic conditions (AORC) in the US was approximately $128 billion equalling 1.2% of the 2003 US gross domestic product. Direct costs totalled $80.8 billion (i.e., medical expenditures) and indirect costs were $47.0 billion (i.e., lost earnings). A US study in 2009 estimated costs due to hospital expenditures of total knee and hip joint replacements to be $28.5 billion and $13.7 billion respectively. When compared to age and gender matched peers, patients with OA have higher out of pocket health-related expenditures with the average direct costs of OA per patient estimated at approximately $2,600 per year. Additionally, job-related indirect costs due to loss of productivity have been estimated to cost from $3.4 to $13.2 billion per year. These figures are likely to be far greater in 2016 given the increasing prevalence of OA, the ageing population and the greater demands for and costs of medical and surgical interventions.

Presently there are no drugs approved that can prevent, stop, or even restrain progression of OA. Moreover, the available medications that promise to mitigate the pain of OA have a number of risk/benefit considerations. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with a clinically relevant 50 –100% increase in the risk of myocardial infarction or cardiovascular death compared with placebo [CNT Collaboration]. As a consequence of these treatment related adverse events and the paucity of other effective treatments, there is an urgent need for clinical studies of new and existing agents that might intervene in the pathophysiology and progression of OA.

In 2014 an FDA Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics* was released providing the FDA's current thinking on four programs intended to facilitate and expedite the development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition; specifically fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. The FDA first articulated its thinking on expediting the availability of promising new therapies in regulations codified at part 312, subpart E (21 CFR part 312). Qualifying criteria for accelerated approval were a "drug that treats a serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)". The term serious has been defined by the FDA as "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." (21 CFR 312.300(b)(1).

OA has all the hallmarks of a serious condition. It is associated with a range of levels of disability severity from mild, when it may cause intermittent pain with only minimal difficulty performing daily activities, to severe with chronic pain, progressive irreversible structural damage and progressive loss of function, often with associated decline in mental health as well as an increase in mortality when a person is no longer able to walk or live independently. Pain from arthritis is one of the key barriers to maintaining physical activity and can be considered a key factor in onset of frailty in the elderly. The impact of OA is multi-factorial and depends on different contexts. Disability and loss of function associated with OA is higher in women, those with lower education levels, and the socially disadvantaged. Those reliant on manual labor, weight-bearing, or positions that involve walking or knee bending for their livelihood, are also more affected by the disability associated with OA.

While there are numerous non-pharmacologic and pharmacologic interventions for OA, and integrated models of patient-centered multi-disciplinary care have been shown to reduce pain and improve function and quality of life among individuals with OA, we have no known cure or proven strategy for reducing progression from early to end-stage OA. We have no proven remedy for preventing the need for total hip or knee joint replacement, which is the end result for millions of OA patients worldwide. It is well documented that the actual rate of total joint replacement may significantly underestimate the true need. Many individuals may be in a health state that would be considered severe enough for total joint surgery, but a variety of personal and system factors are barriers to appropriate care. Further, it is also recognized that undergoing a joint replacement does not equate with remission or reversal of disability, but rather a lessening of disease severity in the replaced joint; it does not solve the problem. Most people continue to suffer some physical impairment following joint replacement and while there are improvements in pain and physical function, they do not reach the comparable level of their population peers. As many as 20-30% continue to experience pain and disability after total joint replacements and one in five require joint replacement in another joint within two years.

OA is also associated with increased comorbidity. A recent systematic review found people living with OA had a pooled prevalence for overall cardiovascular disease pathology of 38.4% (95% confidence interval (CI): 37.2% to 39.6%) and were almost three times as likely to have heart failure (relative risk (RR): 2.80; 95% CI: 2.25 to 3.49) or ischemic heart disease (RR: 1.78; 95% CI: 1.18 to 2.69) compared with matched non–OA cohorts. In addition, OA significantly limits a person's ability to self-manage other conditions, such as diabetes, and hypertension given that OA related pain is associated with reduced physical activity, which in turn is associated with increased all cause mortality. The presence of these comorbidities present contraindications to the use of existing OA therapies such as NSAIDs. Compared with the general population, people with OA have shown excess all cause mortality (standardized mortality ratio 1.55, 95% confidence interval 1.41 to 1.70). The more severe the walking disability, the higher was the risk of death (p value for trend <0.001), largely due to cardiovascular disease.

Global and national health policies need to urgently address the rising burden of OA.

OA has the potential to deny the sufferer the basic human rights as outlined in the United Nations Charter for Rights of Persons with Disability. OA sufferers should have the right to life, to accessibility to activities, to work, to be mobile, to be independent and be part of the community. OA-related disability threatens these rights. Access to interventions to prevent this threat are urgently needed.

In the 2015 World Health Organization(WHO) publication World Report on Ageing and Health, "healthy ageing" was defined as 'the process of developing and maintaining the functional ability that enables well being in older age. Functional ability comprises the health-related attributes that enable people to be and do what they have reason to value.' It is clear that the pain and loss of mobility associated with OA becomes more apparent as people age and hence, people with OA are denied the right to healthy ageing.

The World Health Organization Global Disability Action Plan 2014-2021, also calls for 'better health for all people with disability' and recognizes disability as a human rights issue.

The following White Paper provides an in-depth review of the current literature and analyses of numerous OA cohorts, all supporting the designation of OA as a serious disease with no known cure and no interventions currently available to stop the progression or therapies to manage the pain and loss of mobility with an acceptable benefit:risk profile.

INTRODUCTION

Osteoarthritis (OA) is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness [1]. The illness is characterized by joint pain, swelling and stiffness that leads to activity limitations, participation restrictions, sleep interruption, fatigue and depressed or anxious mood, and ultimately loss of independence and reduced quality of life.

The global impact of OA constitutes a major challenge for health systems in the twenty-first century and in the coming years. In 2005, an estimated 26.9 million US adults were estimated to have OA, up from 21 million in 1990 [2].

OA accounted for 2.4% of all years lived with disability (YLD) and was ranked as the 10th leading contributor to global YLDs [3]. The global prevalence of hip and knee OA is approaching 5%[4] and is destined to increase as the population ages. In addition, obesity rates are rising globally, and as obesity is a strong risk factor for knee and may also increase rates of hip, hand and spinal OA, rates of these painful conditions with their associated disability and loss of function will continue to increase.

This is well demonstrated by trends in YLDs from 1990 to 2013 [5] that show OA, with a 75% increase in YLDs, ranked as the third most rapidly rising condition associated with disability (just behind diabetes at 135% and dementia at 84%). In this most recent update of Global Burden of Disease, (GBD 2013), figures estimated that 242 million people were living in the world with symptomatic and activity limiting OA of the hip and /or knee, accounting for 13 million YLDs [5]. Yet it is also recognized that these figures are likely to be an underestimate of the true global burden of OA [6], in particular as these rates only consider hip and knee OA, not OA at other sites.

The economic burden on patients and society is high in every country that it has been estimated. In the United States (US) in 2003 the total costs attributable to arthritis and other rheumatic conditions (AORC) was approximately $128 billion and equalled 1.2% of the 2003 US gross domestic product. $80.8 billion were direct costs (i.e., medical expenditures) and $47.0 billion were indirect costs (i.e., lost earnings)[7]. In 2009 another US study estimated costs due to hospital expenditures of total knee and hip joint replacements respectively, to be $28.5 billion and $13.7 billion[8]. Patients with OA have also been shown to have higher out of pocket expenses for health-related expenditures when compared to age and gender matched peers. The average direct costs of OA for each patient has been estimated to be approximately $2,600 per year[9]. Job-related OA costs and indirect costs due to loss of productivity were estimated to cost from $3.4 to $13.2

billlion per year[10]. These figures are likely to be far greater now given the increasing prevalence, the ageing population, and the greater demands for medical and surgical interventions.

OA has all the hallmarks of a serious condition [11]. It causes both premature ageing with loss of functioning in society; as well as premature mortality with persons with OA having an increased risk of dying than their age and gender matched peers. OA related disability limits one or more of a person's major daily life activities such as walking, eating, communicating or caring for oneself or ones family. OA has the potential to deny the sufferer the basic human rights as outlined in the United Nations Charter for Rights of Persons with Disability. OA sufferers should have the right to life, accessibility to activities, to work, to be mobile, to be independent and be part of the community. OA related disability threatens these rights. Access to interventions to prevent this threat are urgently needed.

In the recent WHO publication, World Report on Ageing and Health[12], "healthy ageing" was defined as '…the process of developing and maintaining the functional ability that enables well being in older age. Functional ability comprises the health-related attributes that enable people to be and to do what they have reason to value.' It is clear that the pain and loss of mobility associated with OA becomes more apparent as people age and hence people with OA are denied the right to healthy ageing.

The WHO Global Disability Action Plan[13] also calls for 'better health for all people with disability' and recognizes disability as a human rights issue.

OA is associated with a range of levels of severity of disability from mild impact, when it may cause intermittent pain with only minimal difficulty performing daily activities, to severely disabling chronic pain and loss of function, often with associated decline in mental health when a person is no longer able to walk or live independently. Pain from arthritis is one of the key barriers to maintaining physical activity and can be considered a key factor in onset of frailty in the elderly [14-17].

While there are numerous non-pharmacologic and pharmacologic interventions [18] and integrated models of patient-centered multi-disciplinary care that have been shown to reduce pain and improve function and quality of life among patients with OA [19], we have no known cure or proven strategy for reducing progression from early to end-stage OA. We have no proven remedy for preventing the need for total knee joint replacement that is the end result for millions of patients worldwide. Global and national health policies need to urgently address the rising burden of OA.

OA has a significant impact on day-to-day functioning and, although the levels of pain and disability may fluctuate, it has no known cure or spontaneous remission and is associated with irreversible structural damage and progression over time.

The impact of OA is multi-factorial and will depend on different contexts. OA can be the cause of acute and chronic pain and burden in other health domains. The resulting physical limitations may lead to loss of participation and withdrawal from usual social, community and occupational activities [14]. Disability and loss of function associated with OA is higher in women [20,21], those with lower education levels [22] and the socially disadvantaged [23]. Those reliant on manual labor, weight-bearing, or positions that involve walking or knee bending for their livelihood, are also more likely to be affected by the disability associated with OA [24].

People living with OA have greater pain, suffering, disability, fatigue and activity limitation and loss of participation than seen in age-matched peers. While fatigue has been identified as a major factor in rheumatoid arthritis (RA), it has been shown to be important in OA as well. In a recent study OA participants reported greater pain, disability, depression and sleeplessness than those with RA[25].

People with OA have greater participation restriction and activity and work limitation than those without OA.

OA progresses at varying rates but will progress in all people. People who have OA in multiple joints, have a strong family history, are overweight, work in load bearing occupations or with repeated joint injury, progress at a faster rate. Men and women of normal body weight progress to end-stage OA requiring knee replacement at a rate of 1.2% per 6 year follow-up for 45-55 year olds, increasing to 5.1% for those aged 75 years and over. The rate of progression among those who are obese ranges from 3.5% up to 9% per year for 45-55 year olds and those aged 75 years and over respectively (unpublished Communication Cicuttini, FM & Fellow). It is well documented that the actual rate of total joint replacement is likely to significantly underestimate the true need and many others will be in a health state that would be considered severe enough for total joint surgery, but a variety of personal and system factors are barriers to the appropriate care. However, it is also recognized that undergoing a joint replacement does not equate with remission or reversal of disability, but rather a lessening of disease severity. Most people continue to suffer some physical impairment following joint replacement and while there are improvements in pain and physical function, they do not reach the comparable level of their population peers [26,27]

OA is associated with increased comorbidity. A recent systematic review found people living with OA had a pooled prevalence for overall cardiovascular disease (CVD) pathology of 38.4% (95% confidence interval (CI): 37.2% to 39.6%) and were almost three times as likely to have heart failure (relative risk (RR): 2.80; 95% CI: 2.25 to 3.49) or ischemic heart disease (RR: 1.78; 95% CI: 1.18 to 2.69) compared with matched non–OA cohorts. In addition, OA significantly limits a person's ability to self-manage other conditions, such as diabetes, hypertension and coronary heart disease given that OA related pain is associated with reduced physical activity. Further, the presence of these comorbidities may present contraindications to the use of existing OA therapies such as NSAIDs.

OA is associated with increased mortality, both directly as well as due to its associated comorbidities. Compared with the general population, people with OA had a 55% increase in all cause mortality (standardized mortality ratio 1.55, 95% confidence interval 1.41 to 1.70). The more severe the walking disability associated with OA, the higher was the risk of death (p value for trend <0.001), largely due to cardiovascular disease.

No cures are available and current treatments for OA (both surgical and non-surgical) carry a risk of morbidity and mortality due to adverse effects of the interventions. NSAIDs have been associated with clinically relevant twofold to fourfold increases in the risk of myocardial infarction, or cardiovascular death compared with placebo[28,29]

OSTEOARTHRITIS IS HIGHLY PREVALENT

OA affects 240 million people globally. Worldwide estimates are that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA [30]. The global prevalence of combined symptomatic and radiographic OA of the knee and hip from the GBD 2013 Study was 3.8%, ranging from 2.3% in males to 4.5% in females [5]. In high income countries, prevalence was higher at 7.0%; 4.9% in males and 9.1% in females.

The prevalence of OA knee in North America, from GBD 2010 data, was 4.15% overall; 3.5% in males and 5.06% in females. OA hip prevalence rates were 1.91% overall; 1.64% in males and 2.15% in females [4]. **Figure 1** shows that the prevalence of hip and knee OA in males and females increases with age in all global regions [4]

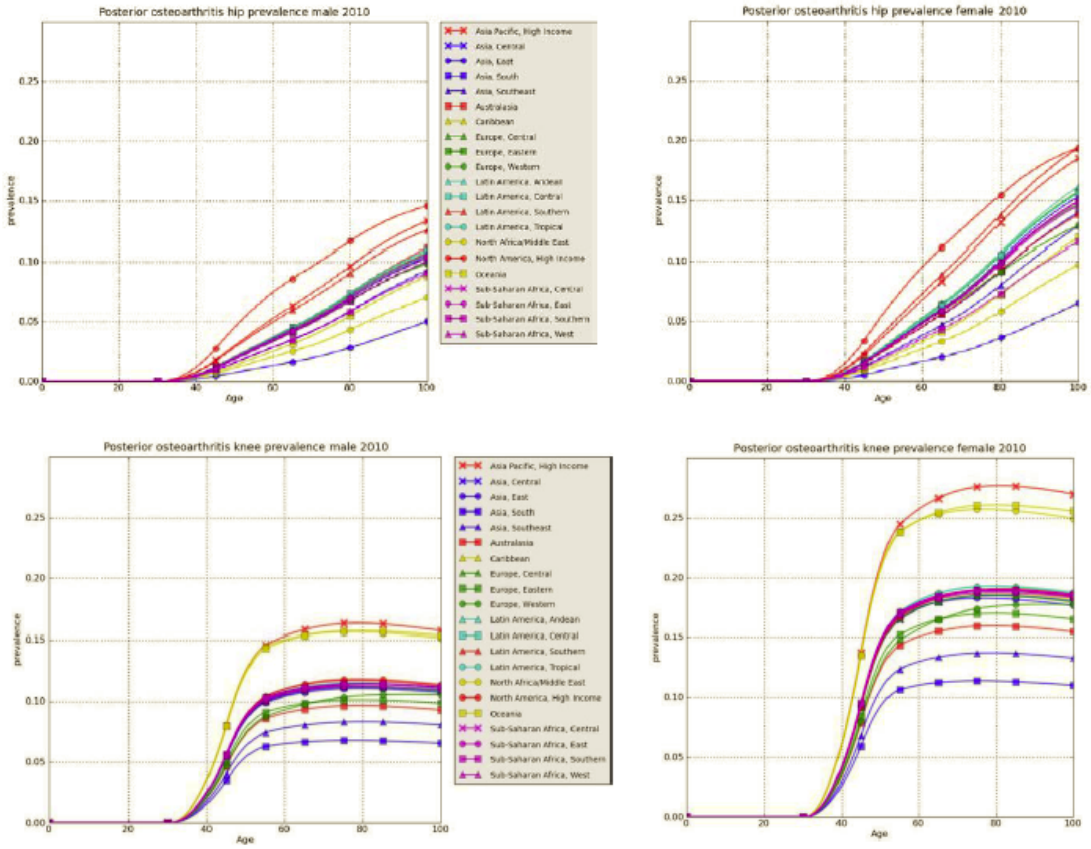


Figure 1: GBD 2010 prevalence of hip and knee OA by gender for global regions

The CDC has reported that overall in the US in 2005, OA affected 13.9% of adults aged 25 years and older. It is known that prevalence increases with age, and for those aged 65 years and over, the prevalence was 33.6%, amounting to approximately 12.4 million people. In 2005, an estimated 26.9 million US adults were estimated to have OA, up from 21 million in 1990 (which is believed to be a conservative estimate)[2]

OSTEOARTHRITIS IS INCREASING

The prevalence of OA is increasing, and with an increase in risk factors for OA, this increasing prevalence of OA is expected to continue.

Within the US, the prevalence of doctor-diagnosed arthritis, which includes OA, is expected to increase in the coming decades (**Figure 2**). By the year 2030, an estimated 67 million adults (25% of the projected total adult population) aged 18 years and older will have doctor-diagnosed arthritis, compared with the 52.5 million adults in 2010-2012 [31].

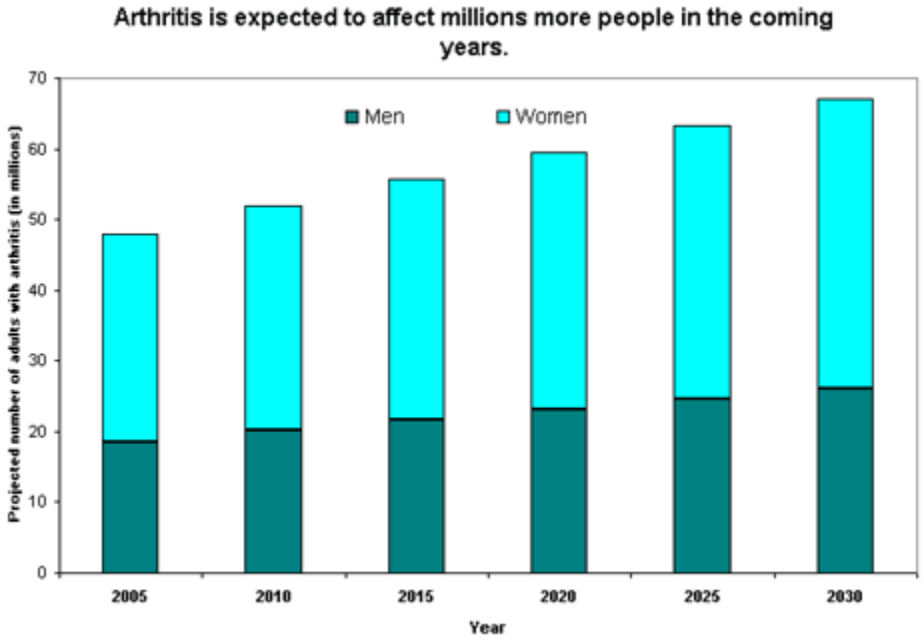


Figure 2: Projected Prevalence of Doctor-Diagnosed Arthritis Among U.S. Adults Aged18 Years and Older, 2005-2030.

Data Source: 2003 National Health Interview Survey; 2030 Census projected population.
http://www.cdc.gov/arthritis/data_statistics/national-statistics.html

RISK FACTORS FOR OSTEOARTHRITIS ARE INCREASING

Obesity and high body mass index are important risk factors for OA. Obesity is associated with the incidence and progression of OA of both weight-bearing and non weight-bearing joints. [32] Since 1980, worldwide obesity has more than doubled. In 2014, 39% of adults aged 18 years and over were overweight, equivalent to more than 1.9 billion adults and 13% were obese, equivalent to over 600 million people [33].

GBD 2013 data showed that global all-age obesity increased by 26% from 2000 to 2013. Obesity also ranked as the number three risk factor for DALYs in 2013, up from a rank of 5 in 2000.

Both within the US and Europe, adults with OA are significantly less likely to meet the recommended levels of physical activity compared to adults without OA. After lifestyle factors, this could also be explained by the fact that people with OA tend to avoid physical activity because activity induces pain. However, decreased physical activity levels might lead to decreased muscle strength and stability of joints, which have been shown to be important risk factors for the onset and the course of OA [34].

Globally, around 23% of adults aged 18 and over were not active enough in 2010 (men 20% and women 27%) . In high-income countries, 26% of men and 35% of women were insufficiently physically active, as compared to 12% of men and 24% of women in low-income countries [35].

Low physical activity as a risk factor showed a 20% increase from 2000 to 2013 (GBD 2013). It was ranked as the number 17 risk factor in 2013, up from 21 in 2000.

While low physical activity is a problem globally, over the past few decades there has been an increase in participation in both youth sports and recreational activity among all ages. This has resulted in an increase in both acute and chronic musculoskeletal injuries, with joint injury being the most common risk factor for OA development in young adults [36]. As life expectancy continues to increase, the span over which adults participate in such physical activities is also increasing. Therefore, the incidence of knee injuries among older adults can also be expected to increase[37].

OSTEOARTHRITIS IS ASSOCIATED WITH SIGNIFICANT MORBIDITY

Hip and knee OA are ranked 13th globally for years life lost due to disability (YLDs), and 17th in the US [38]. The mean YLDs associated with OA were estimated to be more than 12 million, and this represented an increase of 75% from 1990 to 2013 [39].

OA was reported to be the 4th fastest increasing condition, behind diabetes (136%), alzheimers (92%), and other musculoskeletal (MSK) conditions (79%). It should be noted that a considerable percentage of 'Other MSK' are due to OA at sites other than hip or knee, or due to knee and hip pain secondary to OA which is not yet evident on radiographs, so the burden of OA is likely to be much higher.

Low back pain was ranked as the number one condition in terms of YLDs, and neck pain as number four globally[38]. Within the US spinal pain was ranked number one, other MSK problems number three and neck pain ranked 7th. A considerable percentage of the pain from these aforementioned conditions is likely to be attributable to osteoarthritic changes of the spinal and other peripheral joints. Falls were ranked 9th and it is recognized that OA will increase the risk of falls [40]. OA of the hip and/or knee alone was ranked 17th.

Figure 3 below demonstrate the rankings of YLDs globally and within the US.

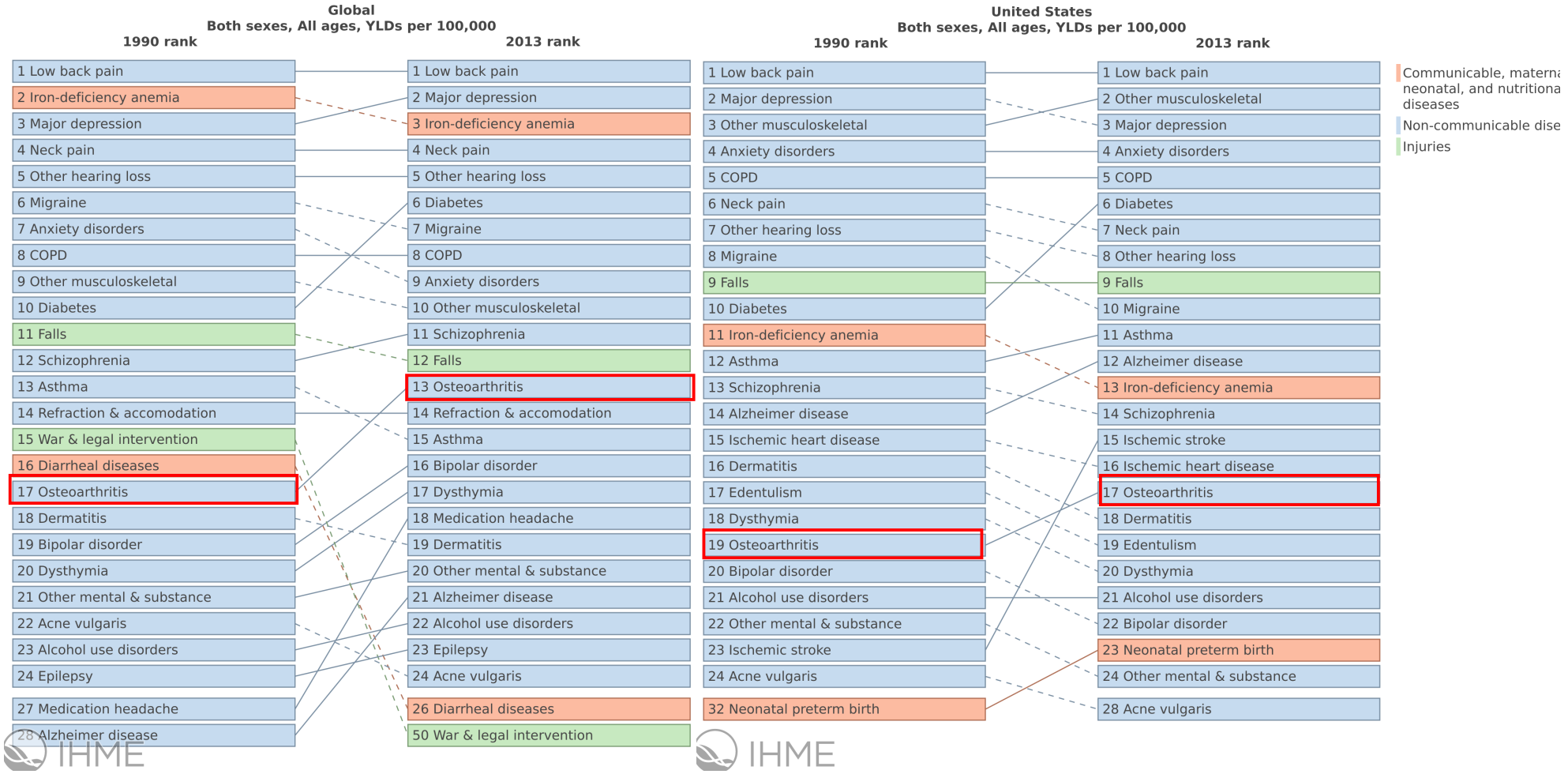


Figure 3: Rankings of YLDs globally and within the US, 1990 and 2013

(source: IHME http://vizhub.healthdata.org/gbd-compare/)

To put the YLDs and Disability Adjusted Life Years (DALYs) of OA within the US into perspective, **Table 1** below shows the figures of other conditions that may also be considered serious.

Table 1: GBD 2013, USA, YLDs and DALYs, OA and possible comparators

Disorder	YLDs		DALYs	
	% of total	**95% CI**	**% of total**	**95% CI**
Osteoarthitis*	1.60	1.22 – 2.02	0.77	0.56 – 1.02
Low back and Neck Pain#	14.64	12.82 – 16.93	7.05	5.51 – 8.70
Other MSK conditions#	6.43	5.10 – 8.04	3.29	2.55 – 4.17
Diabetes Mellitus	4.27	3.58 – 5.01	3.51	3.13 – 3.92
Alzheimers Disease & other dementias	2.11	1.74 – 2.47	3.34	2.85 – 3.85
Ischemic heart disease	1.63	1.44 – 1.84	9.08	8.01 – 10.61
Bipolar Disorder	1.15	0.79 – 1.56	0.55	0.37 – 0.77
Epilepsy	0.81	0.51 – 1.19	0.47	0.32 – 0.64
Rheumatoid arthritis	0.68	0.56 – 0.80	0.37	0.30 – 0.44
Multiple sclerosis	0.34	0.27 – 0.41	0.34	0.25 – 0.39
HIV/AIDS	0.11	0.062 – 0.167	0.052	0.34 – 0.72
Hypertensive heart disease	0.075	0.064 – 0.087	0.68	0.50 – 0.83
Leukemia	0.065	0.54 – 0.077	0.56	0.49 – 0.65

* Hip and knee OA only
# a considerable proportion of this conditions would be attributable to OA

Accounting for 1.6% of the total YLDs, OA contributes similarly to ischemic heart disease. It is slightly higher than for bipolar disorder, but considerably higher than HIV/AIDS and rheumatoid arthritis.

SOME ISSUES AFFECTING THE "TRUTH" OF OA BURDEN

These GBD data only include hip and knee OA, not allowing for the considerable burden of OA at other sites, such as the hands and feet that impact dexterity, strength and mobility. As such, with both the prevalence and the attributable disability impact underestimated, the real burden of OA is likely to be considerably higher.

In the recent GBD2013 Lancet articles, the authors calculated a Data Representativeness Index (DRI) which refers to the global availability of prevalence and incidence data for different health conditions. OA had a low (18.1%) coverage indicating that many countries of the world do not have OA data available and thus the estimates may not reflect the true burden. Overall MSK has a DRI of 51.1% compared with diabetes 98.4%, cardiovascular 86.2%, neoplasms 82.4%, and mental health and substance abuse 67.6%. The levels of data availability are particularly low in Sub-Saharan Africa, Central Asia, Carribbean and the Balkans.

DEFINITION OF OA SEVERITY

Using available data from literature searches and unpublished datasets, patient reported health outcomes can be assessed in terms of quartiles of measures. Drawing from published community-based cohorts, it has been suggested that the highest quartile of the Western Ontario and McMaster Universities Osteorthritis Index (WOMAC) be classified as severe; therefore a WOMAC score of >13 on the 0 to 20 scale is "severe". Using this method and definition of severe based on WOMAC score, 2% of all people in high-income countries were defined as severe for the purpose of GBD 2010 YLD estimations[4]. This would correspond to approximately 6.4 million US citizens living with severe OA.

Recently, the lay descriptions used to define the levels of severity and subsequent disability weights in the GBD 2010 Study have been presented to the French KHOALA cohort[41] (data in **Table 2**). Here participants were asked to indicate which lay description of OA best described them. While the earlier GBD study estimated 2% as severe, a higher percentage of the French KHOALA cohort (13.6%) classified themselves as severe, which would correspond to approximately 43 million people in the US. These definitions showed validity with existing standardized measures of disease, with those in the severe category of disease reporting significantly worse levels of pain, stiffness and function, and poorer performance on walking times. These sufferers are likely to contribute to the greatest component of arthritis related health expenditure.

While almost half of the cohort (46.7%) considered themselves to be in the "mild" category of OA, almost 14% considered themselves to align with the "severe" description. Mean age was similar across the levels.

There was a significant trend for the WOMAC, EQ5D (a preference-based measure of health status), 0-100 Visual Analog Scale and maximal walking time to decline as the self-reported level of severity moved from none through mild and moderate to severe. Those who reported "no pain or disability" reported similar scores on the validated measures to those who indicated they aligned with the "mild" OA description.

Table 2: Self-reported severity of OA within French cohort

N=569	No pain. no difficulty N=49 (16.0%)			Mild OA N=135 (44.0%)			Moderate OA N=80 (26.1%)			Severe OA N=43 (14.0%)			
	N	**%/mean**	**SD***	**N**	**%/mean**	**SD***	**N**	**%/mean**	**SD***	**N**	**%/mean**	**SD***	**p****
SOCIO DEMOGRAPHIC													
Sex													0.0804
Male	37	42.0		75	32.5		54	32.7		20	23.5		
Female	51	58.0		156	67.5		111	67.3		65	76.5		
Age at inclusion	88	62.01	8.3	231	60.1	8.2	165	61.7	8.3	85	62.6	7.9	0.0267
Walking distance													
Maximal distance	82	6,411.5	4,463.5	226	5,096.5	4,052.9	158	2,859.7	2,567.1	84	1.059.6	1,604.6	<0.0001
Maximal walking time	85	113.3	94.9	226	89.4	76.6	158	52.9	54.9	83	22.6	21.7	<0.0001
Need for crutch or cane													<0.0001
All the time	0	0.0		4	1.7		9	5.5		14	16.9		
Occasionally	7	8.0		29	12.7		41	25.0		36	43.4		
Never	81	92.0		196	85.6		114	69.5		33	39.8		
Missing	0			2			1			2			
Fall in the last 12 months													0.0003
No	70	80.5		184	79.7		115	70.1		49	57.6		
Yes	17	19.5		47	20.3		49	29.9		36	42.4		
Missing	1			0			1			0			
Number of falls	17	2.7	2.4	47	1.9	2.1	49	1.9	1.2	36	2.6	2.0	0.1897
EQ5D Index (FR) [0; 1]	88	0.9	0.1	226	0.8	0.2	162	0.6	0.2	81	0.4	0.3	<0.0001
EUROQOL: VAS [0; 100]	88	78.6	12.3	229	72.1	15.4	164	63.4	15.3	85	51.6	15.4	<0.0001
WOMAC (Normalised [0,100]													
Function	88	14.7	12.4	231	23.7	14.3	165	38.7	16.7	84	53.9	15.7	<0.0001
Pain	88	13.2	10.6	230	24.9	13.5	163	39.2	14.9	85	55.2	13.9	<0.0001
Stiffness	88	20.7	17.2	231	32.2	16.8	164	44.4	18.7	84	61.0	16.1	<0.0001
Womac Total	88	14.9	11.2	230	24.7	13.2	163	38.9	15.0	83	55.1	14.0	<0.0001

*** standard deviation**
**** Chi-2 test for qualitative variables, Kruskal-Wallis for quantitative variables**

OSTEOARTHRITIS IS ASSOCIATED WITH INCREASED DISABILITY AND ACTIVITY LIMITATION

The primary symptom of OA is pain. This pain is the factor that drives individuals to seek medical attention and has been described as a dull, aching pain that over time becomes more constant. Short episodes of more intense pain are also experienced in many individuals[42]. Focus groups have identified that this OA pain has a significant impact on mobility and function, sleep, fatigue and mood[42].

The impact of arthritis on individuals is significant. Globally, 80% of those with OA will have limitations in movement, and 25% cannot perform their major daily activities of life [30]. Eleven percent of adults with knee OA need help with personal care and 14% require help with routine needs [43].

Arthritis-attributable activity limitations were estimated to affect approximately 22.7 million US adults between 2010 and 2012 [44], which is higher than the 22 million predicted in an earlier 2006 study. Activity limitations were reportedly higher among females and those in the older age groups. Of those with arthritis-attributable activity limitations, 61% were under the age of 65 years, which is equivalent to 13.8 million people. In the US, those under 65 years comprise 83% of the population (**Figure 4**).

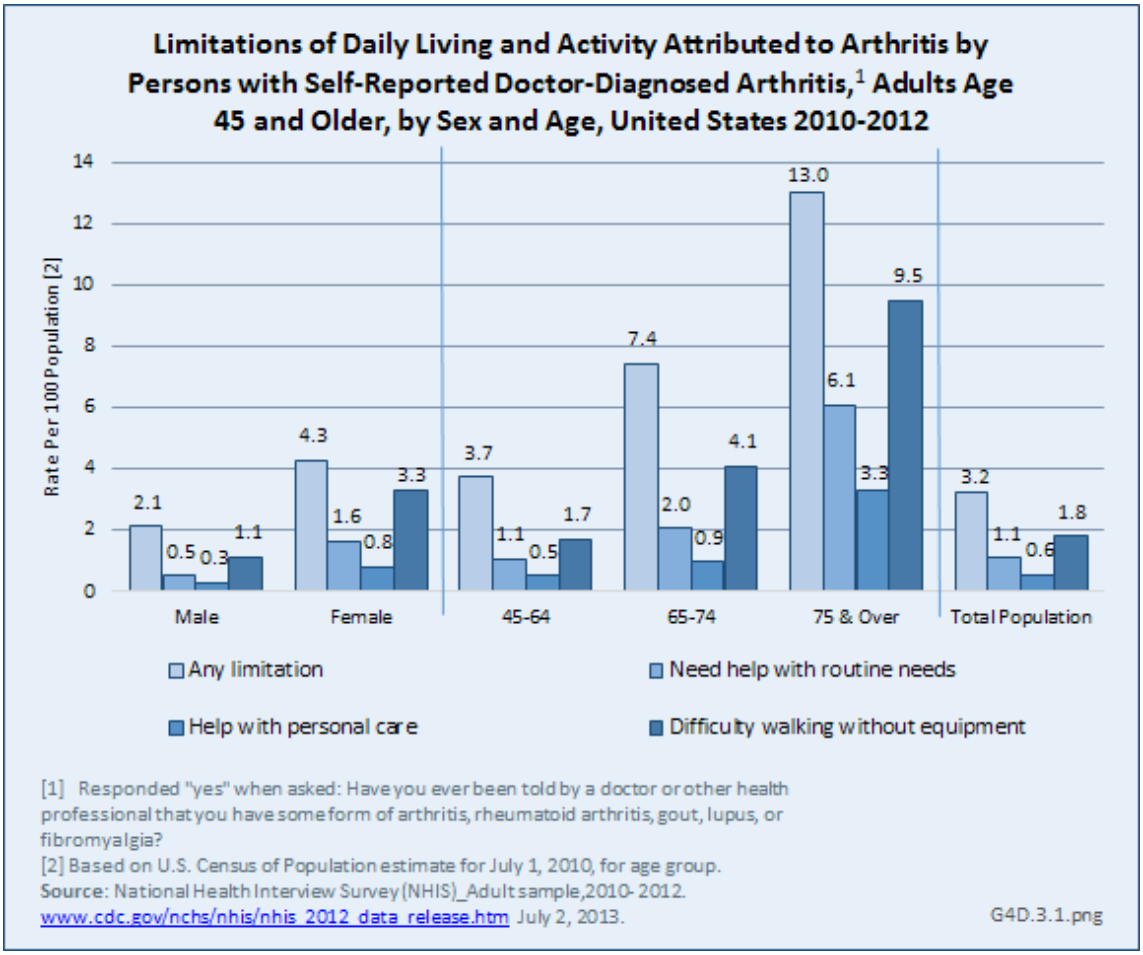


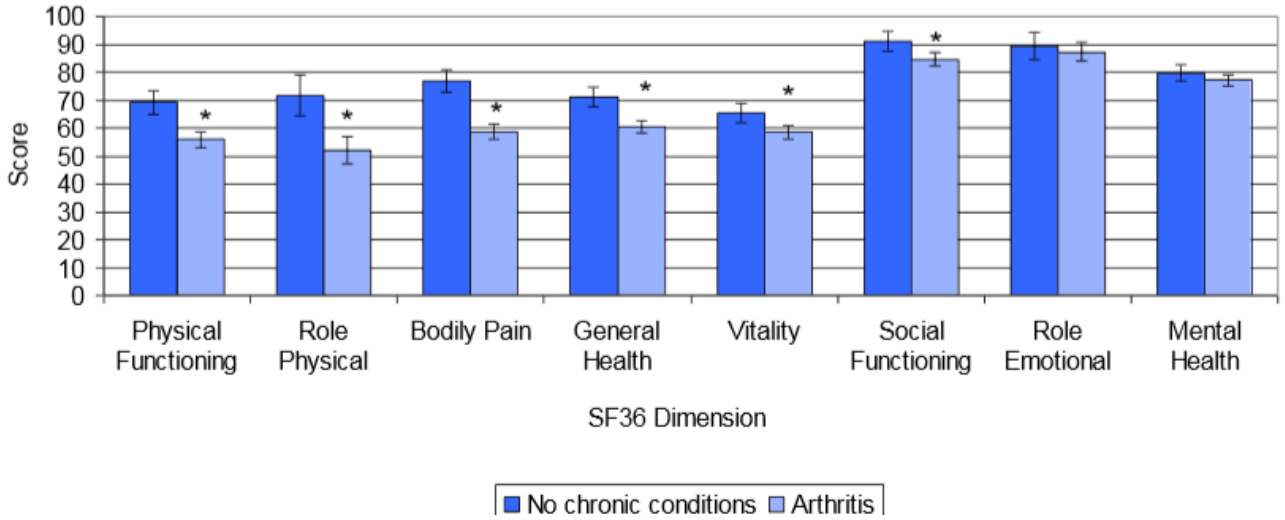
Figure 4: Arthritis-attributable limitations to activities of daily living

Source: BMUS. The Burden of Musculoskeletal Diseases in the United States http://www.boneandjointburden.org/2014-report/ivd3/limitations

Arthritis has a large impact on adults with daily chronic limitations. In a National Adult Survey that reported data from 2010 to 2012, 32% of people who reported difficulty with walking attributed their limitation to arthritis. One quarter of those with limitation with personal care and routine needs attributed their difficulties to arthritis [44]. The impact on activity was greater among females than males, and among older adults.

The SF-36 is a valid and reliable instrument and is a generic indicator of health status for use in population surveys. The NorthWest Adelaide Health Study collected SF-36 data from participants with arthritis and those without a chronic condition. Those with arthrtis scored statistically, significantly lower on the Physical Function, Role Physical, Bodily Pain, General Health, Vitality and Social Function domains than participants with no chronic condition(s) (**Figure 5**)[45]

Figure 5: SF-36 mean scores for participants with arthritis compared to participants with no chronic condition(s).



Source: North West Adelaide Health Study

Using data modeling, it was reported that individuals aged 50–84 years with knee OA experienced losses in quality-adjusted life years (QALYs) over the remainder of their lives ranging from a mean of 1.9 QALYs per person in nonobese individuals with knee OA to 3.5 QALYs for those with knee OA in addition to obesity [46]. This amounts to over 15 million QALYs lost annually due to OA in the US. Similar losses in QALYs are seen in those with other highly morbid conditions such as cardiovascular disease and cancer [47].

An analysis of the literature on disability associated with OA identified recent systematic reviews that assessed disability in hip and knee disorders, knee OA, hand OA and generalized OA. The results of these are summarized in **Table 3.**

Table 3: Data from the literature: systematic reviews of disability associated with OA

Joint affected	Author	Number of studies included	Result
Non-traumatic hip and knee disorders	Van der Waal 2005[48]	40	The impact on health-related quality of life is substantial; Those with knee disorders scored up to 2.5 standard deviations (SD) below standard population especially on physical aspects; Social and mental aspects scored up to 1 SD below reference population. Elderly patients with knee OA in US general population scored 0.3 SDs below reference population on general health. Prior to THA (pooled estimate of 23 studies) scored, on average, 2.5 SDs below population on SF-36 Physical Function and 2.0 SDs below in Role Limitations.
Knee OA	Smith 2014 [49]	32	The majority of studies indicated that people viewed living with OA negatively. Four key factors influenced their attitudes to the condition: the severity of their symptoms; the impact of these symptoms on their functional capability; their attitude towards understanding their disease; and their perceptions of other people's beliefs towards their disease.
Hand OA	Michon 2011 [50]	33	Overall HRQL is a broad concept involving domains beyond pain, function and stiffness. Few data are presently available on hand OA, but it seems to have almost as great an impact as rheumatoid arthritis on HRQL. Pain scores not significantly different between OA and RA.
Generalized OA	Nelson 2014 [51]	24	Generalized OA, with involvement of more than one joint, was associated with poorer function and quality of life and increased disability.

OSTEOARTHRITIS IS ASSOCIATED WITH INCREASED CO-MORBIDITIES AND OTHER CHRONIC DISEASES

In the US, one in four adults has multiple (greater than two) chronic conditions[52]. The most common chronic conditions include heart disease, stroke, diabetes, cancer and OA. For older adults, OA is the disease with the highest co-prevalence of comorbidities[53]. Given that OA has been associated with increased risk of cardiovascular disease and all-cause mortality[54-56], a better understanding of comorbidity in OA is crucial in identifying modifiable risk factors and key areas for intervention.

Overall burden of comorbidity

Various epidemiological studies have examined the prevalence of other chronic conditions in people with OA. For adults with OA, it has been estimated that 59% to 87% have at least one other significant chronic condition [57-61], with the most common being cardiovascular disease, diabetes mellitus and hypertension. While studies have been heterogeneous with respect to patient age, population base and collection of information related to other chronic conditions (patient-reported or physician determined), multi-morbidity clearly affects the majority of people with OA.

People affected by OA have an average of 2.6 moderate-to-severe comorbidities that result in significant impact on their lives (determined by the Cumulative Illness Rating Scale, which groups and rates severity of chronic conditions)[59]. There is a

substantial subset with very high burden comorbidity; 31% of people with OA have five or more other chronic conditions[57]. Those who rate their joint function as worse are most likely to be affected by comorbid chronic conditions[60].

The significance of the impact of this interaction between OA and comorbidities should not be taken lightly. Given that OA co-exists with many important comorbidities, it makes sufferers more prone to adverse effects of our currently available analgesics and anti-inflammatory drugs, leaving care-givers with difficult choices regarding treatment. The development of safe and effective new drugs should be a priority. People with OA are more likely to have many of the other chronic conditions such as diabetes and heart disease that are already recognized by the FDA as serious and concomitant medications may have further negative impact on those conditions. Similarly the pain from OA may significantly restrict the interventions required for their effective management.

A meta-analysis has shown that only a small proportion of people with knee and hip OA meet physical activity guidelines and recommended steps[62]. The presence of symptomatic joint disease may limit the ability of people with obesity to address weight loss through exercise interventions. A focus on the underlying joint disease – the root of the problem – is critical.

Common comorbidities in OA include cardiovascular disease, diabetes, obesity, lung disease, chronic pain, depression, and visual and hearing impairments[63]. The current literature on burden and type of comorbidity in people with OA is presented in **Tables 4 and 5**. The presence of comorbidites in older adults with OA is associated with more pain, greater limitation in daily activities, and a worse prognosis with respect to these limitations[64]. The impact of having OA on the course of other chronic conditions is less well defined. The impact of specific common comorbidities in people with OA will be evaluated here in detail.

Cardiovascular disease

Cardiovascular disease (CVD) affects >1 in 3 American adults and is the most common cause of death for older adults in the developed world[65]. Multiple studies have demonstrated in cross-section a high prevalence of CVD among people with OA. One study found that 54% of people with radiographically-diagnosed knee and hip OA (average age of 66 years) had coexisting CVD[59]. Similarly, in another study of patients receiving total knee replacement (TKR), with an average age of 65 years, 61% had a diagnosis of CVD[58]. The prevalence of CVD has been shown to be double in people affected by knee and hand OA compared to matched controls without OA, in a primary care setting[66]. Another study found the likelihood of having CVD to be 50% greater for people affected by OA in which all joints were considered[67].

There are many potential reasons why OA and CVD commonly co-exist, including shared risk factors such as older age and obesity, and functional limitations resulting from OA. People with OA report more functional limitations in common daily activities[68] and are less likely to achieve physical activity recommendations[62]. There is strong evidence for an inverse relationship between physical activity and CVD[69]. Longitudinally, walking disability in people with OA has been shown to be a potent risk factor for CVD[54]. Regular physical activity may reduce morbidity from CVD and address risk factors[70], highlighting the importance of addressing (and ideally preventing) the joint pain and dysfunction that result in functional limitations in people with OA. There is evidence that treating OA through total joint replacement (knee and hip) reduces the risk of significant CV events[71,72].

In people with established CVD, comorbid OA has been associated with worse physical health[73] and increased burden of symptoms, including chest pain and shortness of breath[74]. Managing these symptoms and effective secondary prevention through participation in cardiac rehabilitation may be limited by the presence of symptomatic OA.

Diabetes Mellitus

Diabetes, a disease that affects 11.3% of Americans and 8.8% of Canadians[75,76], frequently coexists in people with OA. The estimates of prevalence of diabetes in people with knee and hip OA range from 9.7%[63] to 33%[77], with the lower estimate potentially explained by patient underreporting. People with OA are more likely to develop diabetes over time, with a relative risk of 1.32 over 12 years compared to people without OA[78]. Both diseases share risk factors of older age and obesity. Common non-pharmacologic treatment for diabetes includes exercise and weight loss. The presence of symptomatic OA may impact the ability to adhere to these recommendations[79]. Recently published data show that walking difficulty from OA is an independent risk factor for diabetes complications in people with diabetes and OA[80].

Hypertension

Hypertension, a common condition in the developed world, affects over 50% of older adults (>55 years) in the US[65]. Estimates of prevalence of hypertension in populations of adults with OA range from 32 to 81%[63,81-83], using various methods of assessment. When people with OA were compared to matched controls without OA, the prevalence of hypertension was found to be more than double in the group with OA (75% vs 38%)[84]. A cross-sectional analysis of adults aged over 65 years from a primary care setting found that hypertension-OA was the most common combination of comorbidities, affecting over 24% of the population[85]. The presence of joint disease may result in limited physical activity and higher body mass index (BMI) correlating to an increased prevalence of hypertension. People with hypertension may be at higher risk of adverse effects with NSAID use, thereby constraining pharmacological options for OA treatment[86-88].

Obesity and metabolic syndrome

More than one third of adults in the US are obese[89]. Obesity is a major contributor to burden of chronic disease, including heart disease, stroke, type 2 diabetes, hypertension, sleep apnea and certain malignancies. Obesity is associated with increased risk of morbidity and reduced life expectancy[90].

In a study of people with knee OA, where height and weight was measured to calculate BMI, over 57% met the definition of obesity (BMI ≥ 30). Another study that included people with OA at any joint found the prevalence of abdominal obesity (waist circumference >100 cm for men, >90 cm for women) to be 63%, compared to 38% in adults without OA[84]. Presence of the metabolic syndrome, the constellation of cardiovascular risk factors (obesity, diabetes, hypertension and dyslipidemia), has also been shown to be higher in people with OA. It was present in 59% of the OA population compared to 23% of the population without OA[84].

Depression and mental health

Depression is one of the most common mental health conditions, affecting nearly 8% of the population ≥12 years of age in the US[91]. In populations with OA, the prevalence of physician-reported depression ranges from 21% in patients awaiting total joint replacement[81] to over 60% in one cohort of patients with predominantly knee OA when defined by a positive depression

screening questionnaire[92]. Other lower estimates have been reported based on health care claims, electronic medical records (EMR) and patient-reported comorbidities[57,58,77,82].

Depression and pain commonly occur together[93] due to a mutually reinforcing relationship. People with OA and concomitant depression symptoms are less active (decline in steps/day)[94], respond less to systematic depression treatment and have worse pain and depression outcomes[95].

Falls and Fractures

Falls and fragility fractures are a significant source of morbidity and mortality among older adults[96]. Osteoporosis, the bone disease that predisposes to fragility fractures, including fractures of the hip and vertebrae, has been shown to be prevalent in 20 - 33%[60,81,97] of older adults with OA, from both primary care and hospital-based settings. While OA may play a role in the pathogenesis of osteoporosis through reduced weight-bearing activity, OA has been shown to significantly contribute to risk for falls[98,99].

Table 4: Comorbidity studies in osteoarthritis.

Study	Year	Location	Source	Number of subjects with OA	Diagnosis of OA	Mean age	% Female	Data source for co-morbidities?
Ayers *et al.*[58]	2005	USA	Hospital-based	165 (knee only)	Awaiting TKR	68	62.4%	Physician-reported
Gad *et al.*[81]	2012	USA	Hospital-based	382 for TJR (knee and hip), 357 with OA	Awaiting TKR or THR	74	65%	Physician-reported
Gore *et al.*[82]	2011	USA	Medical insurance claims	112,951	Healthcare claims	57	62%	Healthcare claims
Kadam *et al.*[57]	2004	UK	General practice	11,375	Consulted GP for OA within 12 month period	>50 (3 age groups: 50-64, 65-74, 75-84, and 85 years and older		Physician-reported, GP consultations
Leite *et al.*[92]	2011	Brazil	Outpatient clinic	91 (mostly knee, also hand and hip)	ACR clinical criteria, seen by rheumatologist	59	91.4%	Objective measurement of BP, weight, height, fasting glucose and cholesterol profile. Screening questionnaire for depression.
Nielen *et al.*[83]	2012	Holland	General practice	4,040 (knee and hip)	GP coded	69.8	68.7%	GP coded morbidity
van Dijk *et al.*[59] Reeuwijk *et al.*[63]	2008, 2010	Holland	Hospital/ rehabilitation centre	288 (knee and hip)	Radiographic	66	71.2%	Patient reported
Caproali *et al.* [60]	2005	Italy	General practice	29,132	ACR clinical criteria	all patients ≥50 (mean age not provided)	Not provided	Unclear if patient or physician reported
Tuomine n *et al.*[77]	2007	Finland	Hospital-based	893 (knee and hip)	Need for TJR determined by orthopedics, RA/hemophilia /congenital/ fractures excluded	66	63%	Physican-reported (medical record)
Juhakows ki *et al.*[61]	2008	Finland	Outpatient rehabilitation clinic	118 (hip)	KL grade ≥ 1 and meets ACR clinical criteria	66.7	70.3%	Patient-reported

Table 5. Comorbidities in patients with osteoarthritis.

	Ayers *et al.*[58]	Gad *et al.*[81]	Gore *et al.*[82]	Kadam *et al.*[57]	Leite *et al.*[92]	Nielen *et al.*[83]	van Dijk *et al.*[59] Reeuwijk *et al.*[63]	Caporali *et al.* [60]	Tuominen *et al.*[77]	Juhakowski *et al.*[61]
Total number with ≥ 1 comorbidity	83.6%			87%			98.6% (84.4% + at least 1 other mod-to-severe disease)	85%		58.7%
Number of comorbidities per person				1/2 30% 3/4 26% 5+ 31%			4.3 (2.6 moderate-to-severe comorbidity)	2		
Clinical groups:										
Cardiovascular	61.2%	7% CHF 7% Stroke	1.4% MI 10.6% CAD 3.8%CHF 4.9% stroke	36.1%		8.1% (MI 1.5% stroke/TIA 5.9%)	54% (8% severe heart disease or CAD 2.1% stroke)	6% MI/angina	63%	
Hypertension		81%	54.4%			38.5% (use of anti-hypertensive 45%)	31.9%	52%		
Dyslipidemia		63%	52.1%		52.6%	13.3% (use of statins 20.0%)			33%	
Obesity	7.9%	51%			57.1%		23.9%			
Endocrinological/ diabetes	21.8%	22%		12.2%	17.6%	16.5%	46% (9.7% diabetes)	15% diabetes	33% diabetes	
Pulmonary		15%		36.4%			28.8% (15.6% asthma or COPD)	12% COPD	14%	
Other MSK	8.5% RA	19% LBP	32.5% LBP	36%			29.5% LBP (10.1% other rheumatic diseases)		18%	
Peripheral vascular disease/other vasc	17.6%	9%	5.2%							
Gastrointestinal		54% (GERD or PUD)	18.1% GERD	22.1%			65.2% (3.5% PUD)	5% PUD		
Mental health	3.6%	21%	12.4% depression 6.6% anxiety	12.8%	61.5% (positive screening questionnaire for depression)		26.3%		2%	11.4% depression
Cancer		21%		4.5%			2.4%		4%	
Osteoporosis		22%						21%		

OSTEOARTHRITIS IS ASSOCIATED WITH INCREASED MORTALITY AND RISK OF DYING

While the main areas of investigation in OA have been the impact on pain and physical functioning, disability, and healthcare utilization, in recent years the mortality associated with OA has been identified. Globally, aging populations and the growing prevalence of obesity have led to increased population risk for hypertension, dyslipidemia, diabetes, and CVD. A less recognized consequence of these trends is the increasing burden of OA.

In 2008, a systematic review of mortality in OA was conducted, concluding that overall there is an increased mortality rate among those with OA than in the general population [100]. As population changes have occurred since 2008, with an increasing proportion of obese and elderly persons, this review was updated in 2015 with the following recent publications found (**Table 6**).

Table 6: Publications on OA mortality

Study	Year of study	Location	Source	No. of persons with OA	Mean age	Mean duration of follow-up (years)	% women	SMR	Info on causes of death?	Info on risk factors?
Cerhan et al [101].	1995	USA	Radium dial-painting workers	296	57.1	28	100	--	Yes	Yes
Watson et al [102]	2003	UK	GPRD registry	163,274	--	M: 4.7 F: 4.8	62.3	M: 18.5^ F: 15.9^	CV only	No
Haara et al [103]	2003, 2004	Finland	Population-based	Not specified (prevalence rates only)	--	15-17	--	OA in any finger joint not associated with mortality	CV only	Yes
Kumar et al. [104]	2007	UK	Clinic-based	485	--	15	66.2	--	CV only	No
Tsuboi et al [105]	2010	Japan	Population-based	244	67.7	10	68.5	2.316 (1.412-3.801)+	Yes	Yes
Nuesch et al [56].	2011	UK	Population-based	1163	--	14.3	56.7	1.55	Yes	Yes
Cacciatore et al [106]	2013	Italy	Electoral rolls	698	74.8	12	80.1	Frailty but not OA was predictive of mortality	No	Yes
Haugen et al [55]	2013	US	Framingham Heart Study (Original and Offspring cohorts)	726	62.2	14-21	53.8	OA in hand not associated with mortality but associated with heart disease	Yes	Yes
Hawker et al [54]	2014	Canada	Population-based	2156	71.3	13.2 (hip OA) 9.2 (knee OA)	72	--	No	Yes
Liu et al [107]	2015	The Netherlands	GARP study, OCC study	844	60.5	9.9 (GARP) 3.9 (OCC)	85	0.54 (GARP) 0.45 (OCC)	Yes (GARP only)	Yes
Barbour et al. [108]	2015	US	Study of osteoporotic fractures	7889	72.7	16.1	100	1.14#	Yes	Yes
Liu et al [109]	2015	China	Population-based	244	62.1	8	68.3	1.9# (SxOA) 2.2# (radiographic OA)	No	Yes

^ listed as standardised incidence rate (per 1000 patient-years) of all cause mortality
* listed as crude relative risk (RR)
+ listed as odds ratio
# listed as hazard ratio

These data suggest that OA is not simply a degenerative disease, but there is a degree of mortality associated with OA. This review did not include the term "frailty" and its association with OA, but the contribution of frailty to mortality has also been identified. Possible explanations for the excess mortality of OA include reduced levels of physical activity among persons with OA due to involvement of lower limb joints and presence of comorbid conditions, as well as adverse effects of medications used to treat symptomatic OA, particularly NSAIDs.

The severity of OA related pain and disability are significant predictors of future risk for all-cause death. These effects remained after controlling for multiple potential confounders, including obesity and obesity-related conditions, social health determinants and mental health status [54]. Walking disability was a significant predictor of survival in OA – the more severe the walking disability, the higher the risk of death[54,56].

Causes of death in patients with OA are shown in **Table 7**.

Table 7: Causes of death in patients with OA (% total deaths)

	Cerhan et al. 1995 [101]	Watson et al. 2003 [102]	Kumar et al. 2007 [104]	Tsuboi et al. 2010 [105]	Nuesch et al. 2011 [56]	Haugen et al. 2013 [55]	Liu R et al. 2015 [107]	Barbour et al. 2015 [108]
Total no. of deaths	18.6% (55/295)	--	31.8% (154/485)	16.8% (41/244)	38% (438/1163)	32 (28.36)^	4.4% (37/844)	67.7% (5341/7889)
Cardiovascular	36	M: 11.9^ F: 7.6^	35.7; aRR = 1.96 (1.21-3.25)		16		M: 13.5 F: 10.8	26.3
Myocardial infarction		M: 8.3^ F: 4.4^						
Cerebro or cardiovascular disease				7		8 (6,10)^		
Cerebrovascular disease		M: 5.9^ F: 3.2^						
Cancer	36		aRR = 1.00 (0.62-1.61)	5.3	11	8 (6,10)^	M: 8.1 F: 2.4	11.7
Respiratory	0.5			2.5	3.7			
GI	0.7				1.6			1.9
Dementia					1.4			
Poisonings or accidents	7							
Other/unknown	7.8	M: 0.8^ F: 0.5^		2	4.2	15 (13, 18)	43.2	27.8

Most of the excess mortality associated with walking problems in OA is due to cardiovascular causes. There has been no evidence that cancer related deaths and deaths associated with dementia are related to increased walking disability, which suggests that there are other possible explanations for the relation between OA mortality and walking disability. These may be that reduced physical activity may lead to reduced protection

against CVD, or ongoing tissue damage may result in chronic inflammation. This chronic inflammation may be causally involved in various chronic conditions, such as cardiovascular and neurodegenerative disease, diabetes, or cancer [56].

Individual Patient Data Meta-analysis

Traditional meta-analyses are valuable and efficient in terms of time and resources required but suffer from several limitations. They are limited to published data and may therefore suffer from publication biases as negative studies are often difficult to publish. Secondly, most studies will vary in their definitions of exposures, confounders and outcomes, which may add to bias. Hence a review was commissioned and the methods and results appear below in brief. The full analysis is available in (**Appendix 1**). The aim was to conduct an individual patient level (IPD) meta-analysis utilizing original raw data from cohorts and using standardized statistical methods to analyze and produce pooled estimates. IPD meta-analysis, although time consuming and resource intensive, is not dependant on previously published data allowing for a standardized definition of symptomatic radiographic OA (SROA) and analysis using consistent statistical methods.

Methods

Aim: To perform a two-stage IPD meta-analysis of all available population based cohorts to assess whether patients with OA of the hip and knee have an increased risk of premature mortality.

Study Design

This study was designed to look at the relationship between lower-limb OA and all-cause mortality in multiple, prospective, longitudinal, population-based cohort studies from around the world. Subjects were stratified by the presence or absence of OA at baseline and time-to-mortality was compared between groups.

Cohort selection

Cohort studies were identified by a literature review for established longitudinal OA cohorts in the normal population in addition to expert knowledge of available data. Cohorts were selected based on the presence of OA-related pain and radiographic data at baseline. Thirty-three were identified as meeting this criteria and further searches and follow up liaison was conducted to establish the presence of available mortality data for these subjects. Cohorts were *not* selected for whether or not they had already published data on the relationship between OA and mortality. Eight cohorts were identified with data that had pain and radiographic data and were available for analysis (Johnston County, US; SOF, US; MOST, US; Framingham Offspring, US; Chingford, UK, Hertfordshire, UK; ROAD, Japan; Rotterdam, Netherlands, TasOAC Australia). Four further cohorts were identified as having both OA and mortality data, but require further investigation of the usability of raw data (Osteoporotic Fractures in Men (MrOS) [110], Wuchuan OA study [111], The Beijing Osteoarthritis Study [112], Baltimore Longitudinal Study of Aging [113]). Inclusion of these cohorts in future analyses would be beneficial to widen the global scope of this research. Several cohorts ultimately did not have the required detail for categorical OA of the hips and/or knees and are therefore presented in the analysis using pain alone (SOF and Johnston County).

The characteristics of the eight cohorts included in this analysis are described below in **Table 8**. There are three normal population cohorts (Framingham, Johnston County Cohort, and Study of Osteoporotic Fractures (SOF))

[114-116] and one enhanced risk factor cohort (Multicentre Osteoarthritis Study (MOST) from the United States [117]; two population-based cohorts from the United Kingdom (Chingford and Hertfordshire) [118,119]; a Dutch population-based cohort (Rotterdam) [120]; a Japanese population-based cohort (Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) [121]; and an Australian population-based cohort (The Tasmanian Older Adult Cohort (TasOAC)[122]. The majority of cohorts had time-to-event data available for this analysis. The ROAD study had binary mortality event data collected at their year seven follow-up visit and will therefore be presented separately from studies containing time-to-event data. The other key differences between cohorts are the year of baseline visit, length of follow-up and the age of participants at baseline.

Table 8. Cohort characteristics of the included cohorts

Cohort	Country	Year of Cohort Baseline	Original N	% of Women	Baseline Age	Follow-up (years)	Mortality
Chingford	UK	1989	1003	100%	44-67	23	Time-to-event
Hertfordshire	UK	1998	1412	50%	64.9 (2.7)	11	Time-to-event
Rotterdam	Netherlands	1997-99	7983	60%	>55	18	Time-to-event
Johnston County	USA	1991-97	4197	50%	61.1 (10.6)	23	Time-to-event
SOF	USA	1986-88	10000	100%	>65	23	Time-to-event
Framingham	USA	1971-75	5124	50%	55	14	Time-to-event
MOST	USA	2003	3026	60%	62	7	Time-to-event
TasOAC	Australia	2002-04	1099	50%	63.0 (7.5)	14	Time-to-event
ROAD	Japan	2005-07	3040	50%	70.2 (11.1)	7	Binary

Median follow-up for the analyses of these cohorts ranged from 5.6 (5.5,5.8) to 19.8 (19.1, 20.4) years after baseline. There was substantial variability in the age at baseline and the duration of follow up in each cohort, such that the percentage of subjects that dies in each cohort ranged from 2.9 to 57.9% (**Table 9**).

Table 9. Mortality data in cohorts

Cohort	Joint	N	Max Follow-up (years)	Median Follow-up (yrs)	Follow-up, Range	Mortality
Chingford	Knee	683	22.5	19.8 (19.1, 20.4)	0.13 - 22.5	127 (18.6%)
Hertfordshire	Knee	817	11.4	9.6 (8.7, 10.5)	2.32-11.4	67 (8.2%)
Johnston County	Knee	3,762	23.7	11.6 (9.0, 17.7)	0.07-23.7	1,348 (35.8%)
Johnston County	Hip (pain only)	3845	23.7	11.6 (8.9, 17.7)	0.04-23.6	1,393 (36.2%)
MOST	Knee	2906	7.4	5.6 (5.5, 5.8)	0.16 - 7.4	84 (2.9%)
SOF	Hip (pain only)	8055	23.3	16.6 (11.4, 20.5)	0.02 - 23.3	4660 (57.9%)
Rotterdam	Knee	2813	17.8 years	14.3 (9.8, 15.6)	0.2-17.8	1412 (50.2%)
Rotterdam	Hip (pain only)	3795	17.8 years	14.1 (9.2, 15.6)	0.2-17.8	1,972 (52.0%)
TasOAC	Knee	410	13.6 years	6.4 (2.9, 10.6)	0.04-13.6	128 (31.2%)
TasOAC	Hip (pain only)	439	13.4 years	6.4 (2.9, 10.5)	0.04-13.6	136 (31.0%)
Framingham	Knee	886	13.9	11.9 (10.9, 12.6)	1.7-13.9	68 (7.7%)
ROAD	Knee	2354	7			90 (3.8%)

Kaplan-Meier Plots

Example survival estimate curves and 95% CIs are shown for knee SROA and hip symptomatic OA only in Framingham and Johnston County (**Figures 6-12**).

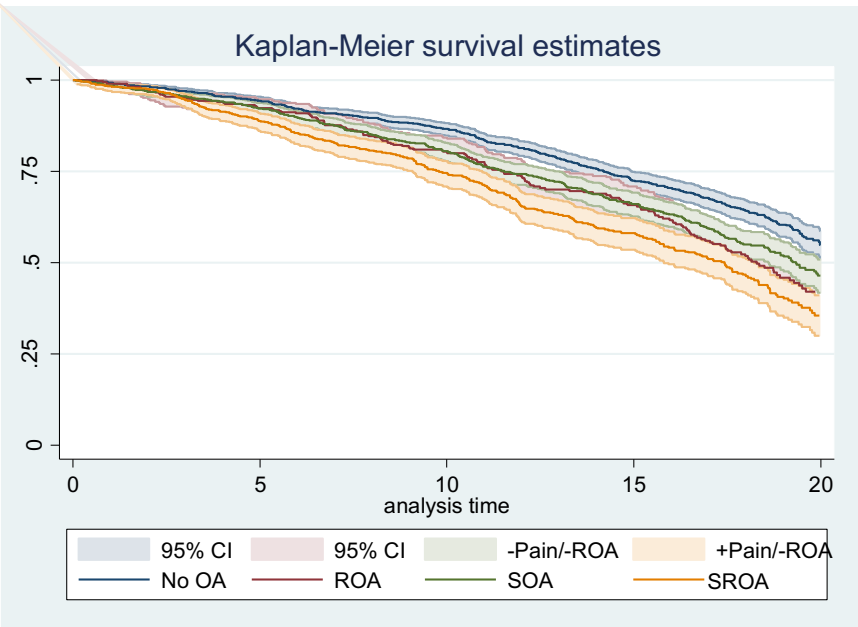


Figure 6. Kaplan-Meier plot for knee SROA in Johnston County cohort (truncated at 20 years follow up)

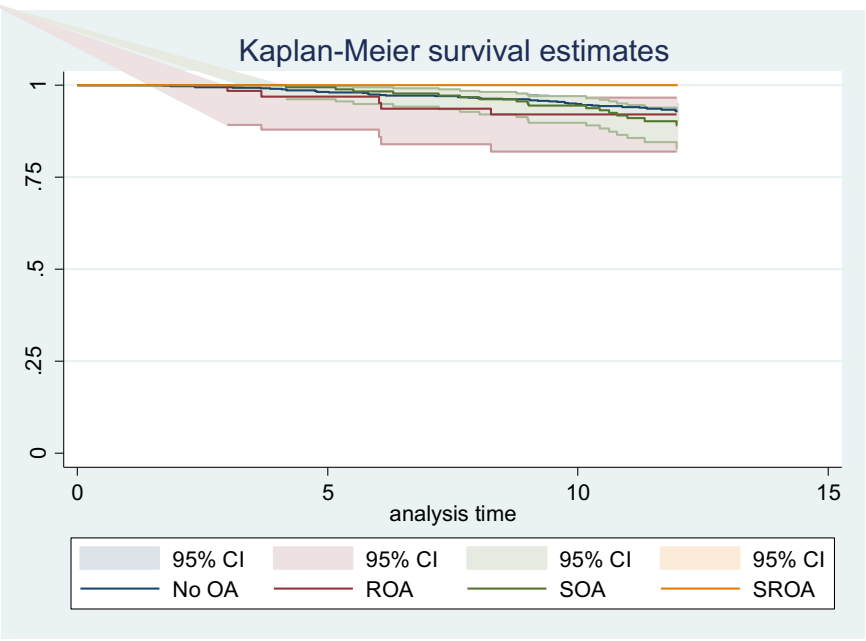


Figure 7. Kaplan-Meier plot for knee SROA in Framingham cohort (truncated at 12 years follow up)

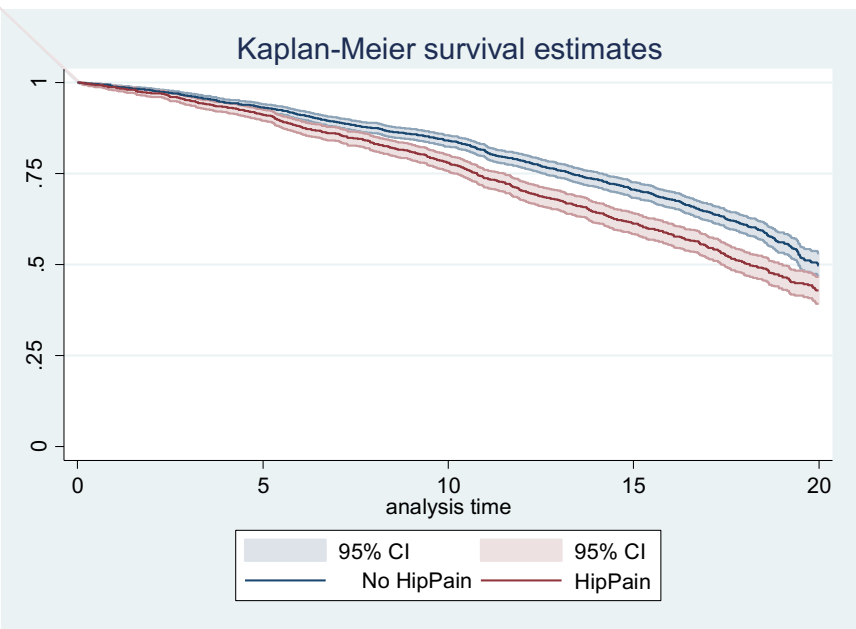


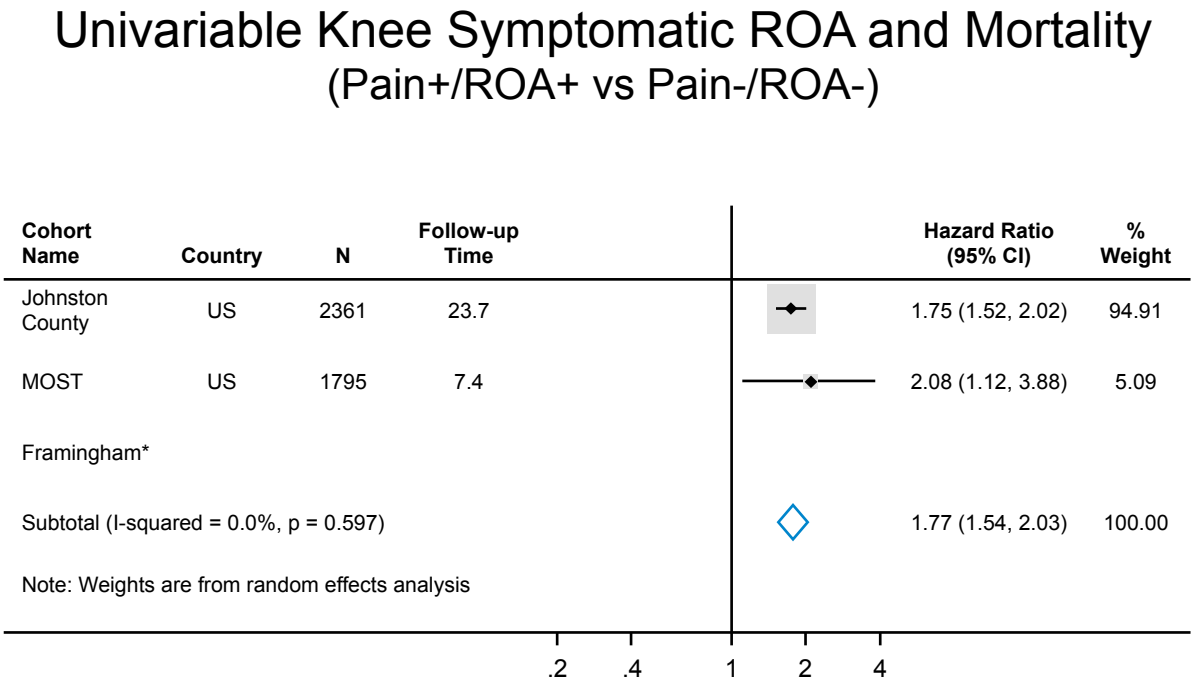
Figure 8. Kaplan-Meier plot for hip pain in the Johnston County cohort (truncated at 20 years follow up)

Meta-analysis of Symptomatic Radiographic Knee Osteoarthritis

This analysis compared subjects who had both pain and radiographic OA in the same joint (Pain+/ROA+) at baseline against subjects who had no OA. It is important to note that this group contained participants who could have reported pain for up to 14 days per month and therefore could have suffered from early/mild OA.

In the unadjusted analysis, subjects with symptomatic radiographic knee OA (SROA) in the MOST cohort had the highest risk of premature death (HR 2.08 [95% CI 1.12, 3.88]), with Johnston County the next highest (HR 1.75

[95% CI 1.52, 2.02]). The pooled estimate for the American subgroup of cohorts was HR 1.75 (95% CI 1.54, 2.03). (**Figure 9**).

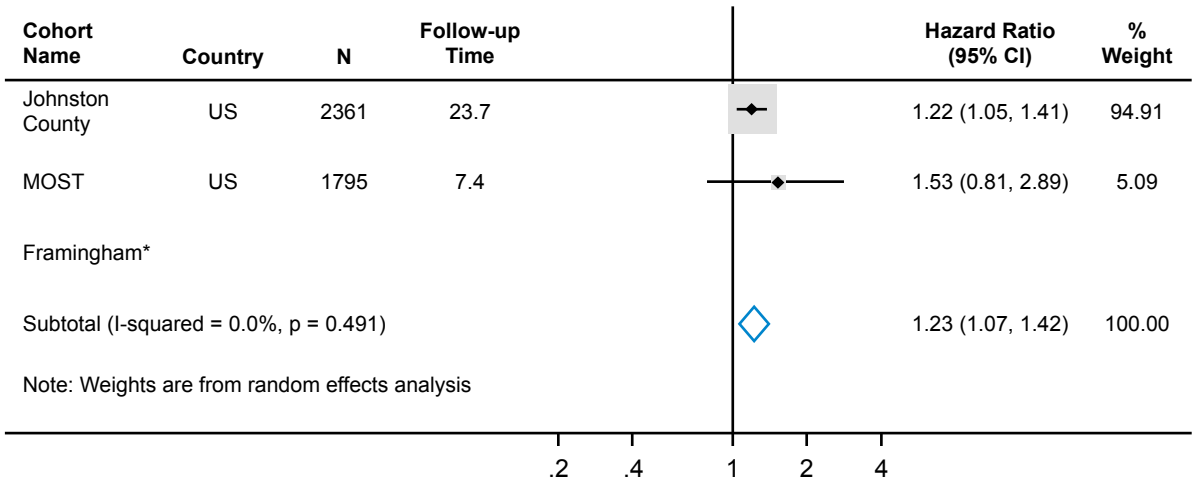


*The Framingham cohort was omitted from this analysis due to the very low number of subjects having the outcome of interest.

Figure 9: **Univariable SROA Forest Plot**

The results of the multivariable analysis, adjusted for age, sex and race, were attenuated slightly in all cohorts. The pooled estimate for the US subgroup showed a 23% increased risk of premature mortality with SROA (95% CI 1.07, 1.42) (**Figure 10**).

These results confirm an increased risk of premature mortality in the US cohorts with an adjusted HR of 1.23 for SROA.



*The Framingham cohort was omitted from this analysis due to the very low number of subjects having the outcome of interest.

Figure 10. Multivariable SROA Forest Plot (adjusted for age, sex, and race)

Symptomatic Hip OA (regardless of ROA status)

This analysis compared subjects who had hip pain (regardless of radiographic OA) at baseline against subjects who had no hip pain.

In the univariable analysis of subjects with hip pain, the data from the US subgroup showed a 22% increased risk of premature mortality (95% CI 1.05, 1.43) (**Figure 11**).

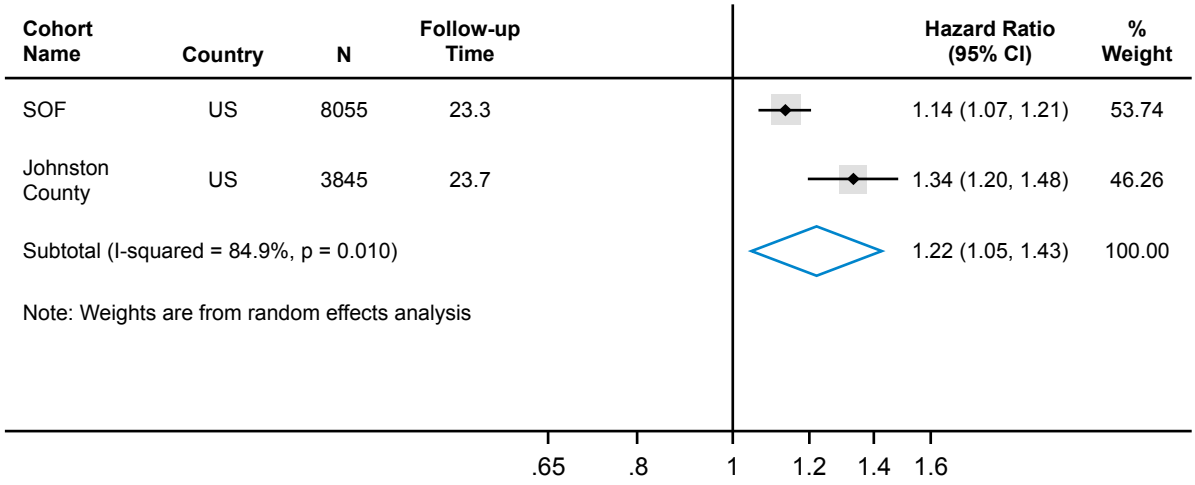


Figure 11. Univariable Hip Pain (regardless of ROA status) analysis

When adjusted for age, sex and race, the US subgroup had a 20% increased risk of mortality (95% CI 1.04, 1.37) (**Figure 12**).

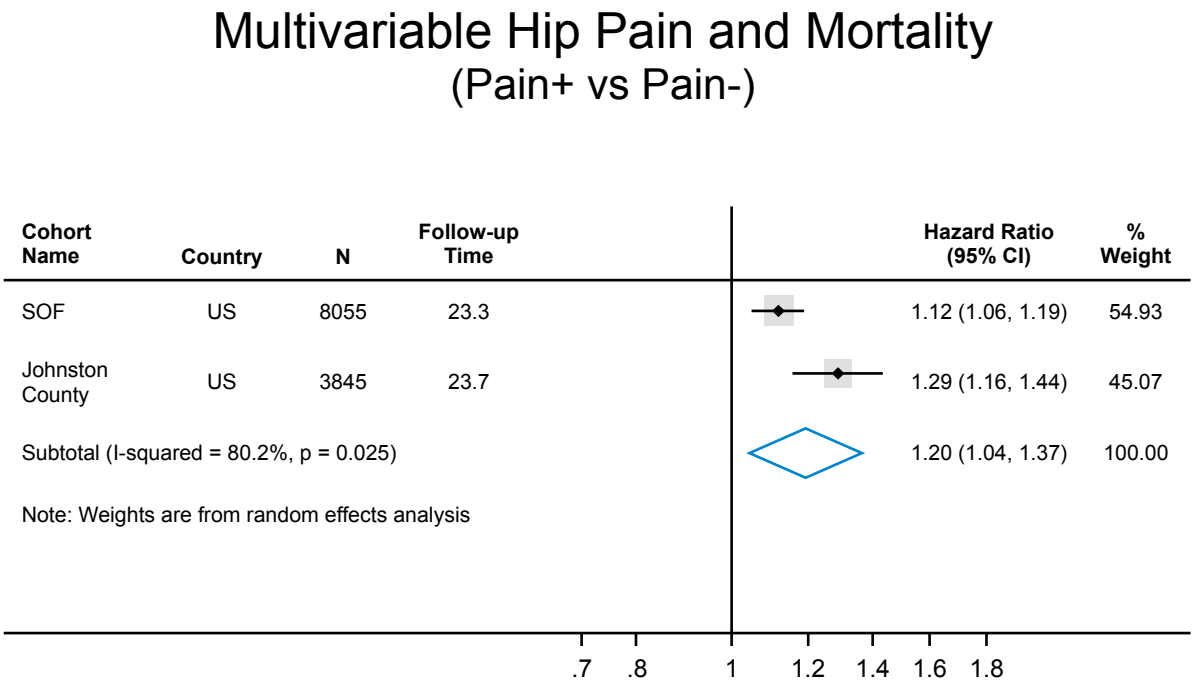


Figure 12. Multivariable Hip Pain (regardless of ROA status) analysis adjusted for age, sex and race

Key Findings

Subjects in the US cohorts with symptomatic radiographic knee osteoarthritis were 23% more likely to die prematurely than subjects free from OA, independent of age, sex and race. US subjects with hip pain had an increased risk of 20% compared to subjects without.

OSTEOARTHRITIS IS ASSOCIATED WITH WORK LIMITATION, INCLUDING PREMATURE WITHDRAWAL FROM THE WORK FORCE AND INCREASED WORK ABSENCES AND SICK LEAVE

OA prevalence is high in those of working age, and the impact of working with symptomatic OA and associated pain and loss of function is substantial. This is especially true for those who are involved in manual labor. In addition to being limited in the type of work activities that can be performed, functional limitations may lead to forced unemployment or early retirement.

Reduced work productivity is typically measured in two ways: as days taken off work (absenteeism) or as self-reported reduced work productivity while at work (presenteeism).

In the US in 2002, arthritis-attributable work limitations were estimated to affect approximately 30% of adults aged 18-64 years with doctor-diagnosed arthritis [44]. Higher rates were seen in those aged 45-64 years, women, non-Hispanic blacks and those with low education or low income. Between 2010 and 2012, 3.8 million people aged 18 years and older with doctor-diagnosed arthritis reported they are "unable to work now due to a health condition". Additionally, 2,1 million people reported they are "limited in the kind or amount of work they can do" [44] (**Figure 13**).

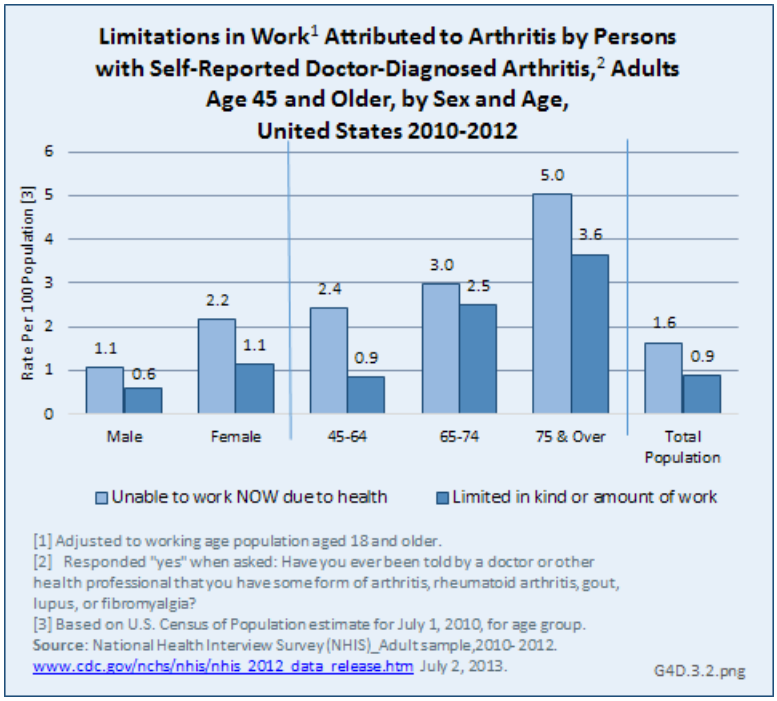


Figure 13: Work limitations attributable to arthritis, US 2010-2012

Source: BMUS. The Burden of Musculoskeletal Diseases in the United States
http://www.boneandjointburden.org/2014-report/ivd3/limitations

A recent systematic review assessed the concepts of presenteeism and absenteesim in OA identified that OA has considerable impact on the ability to participate in paid employment [123]. This review reported:

Absenteeism

- A clinic-based survey found 71% of participants reporting 'reduced' work hours in the past 12 months because of 'osteoarthritis' [124]

- A nationwide survey, found 21% of people with knee osteoarthritis reported 'missed work' ever because of osteoarthritis [125]
- In assessing the mean number of sick days, three studies found a range from 3 to 25 days per year. A fourth study found a mean of 0.5 days absent due to knee pain within the last week [126-129]

Pain is a leading cause of absenteeism related to OA. Investigations of the reasons for absenteeism found a higher number of reported pain days, presence of knee pain or an increase in pain scores were associated with increased absenteeism. Age is also positively associated with absenteeism. Compared with people aged 30 years and below, those aged 45 years and over were approximately twelve times more likely to report absenteeism over a period of 12-months. [130]

Using pooled data from the Medical Expenditure Panel Survey, it was reported that in the US, OA increased annual per capita absenteeism costs by $469 for female workers and by $520 for male workers, the equivalent to approximately 3 lost workdays. This amounts to an aggregate absenteeism cost of $10.3 billion annually (women: $5.5 billion; men: $4.8 billion).

Presenteeism

- Two studies reported presenteeism rates ranging from 66% to 71% [125,131]
- A nationwide survey, found workers with knee osteoarthritis (clinic-based cases) were more likely to report a limited ability to work (66%) when compared with same sex-age working population controls (14%) [125].

As with absenteeism, pain is also associated with presenteeism. Associations were found between knee pain and changes in pain and increased reported presenteeism.

Using four methods of assessing the costs associated with presenteeism, the estimates varied widely, from $700 to $7,000 per worker per year [132]. These estimates are higher than that reported for temporary absenteeism.

OSTEOARTHRITIS IS ASSOCIATED WITH PERSONAL AND SOCIETAL ECONOMIC LOSS

There is considerable personal and societal economic loss associated with OA. Because a cure for OA is not currently available, the disease can be present for decades, leading to further substantive individual and societal loss.

As described previously, a considerable proportion of those with OA retire early due to the pain and disability associated with the condition. Mean per-person earnings losses attributed to OA have been estimated to average $7,548 per year in 2008 to 2011. BMUS have reported that aggregate earnings losses for the 16.1 million people in the US workforce with OA and allied disorders averaged $122 billion in each of the years 2008 to 2011[44] .

Within Australia, the median total accrued personal savings by the age of 65 years of males aged 45-54 who retired early from the work force due to arthritis (not specifically OA), was estimated to be as little as AU$315. This is considerably less than the median accrued personal savings for those who remained in the workforce full time, whose estimated personal savings at age 65 years was AU$339,121[133]. The median weekly income of those who retired early due to arthritis (not specifically OA) was AU$260, compared with those employed full time

who were likely to earn on average five times this amount. Nationally, AU$3.8 billion in private income was lost to these retired individuals annually, and they paid AU$394 million less in personal income tax[133].

OSTEOARTHRITIS IS ASSOCIATED WITH INCREASED HEALTH SERVICES UTILIZATION AND COST TO INDIVIDUAL AND SOCIETY

Painful OA drives health care use. Data from the 2010 NHCS surveys on ambulatory care indicates that more than 100 million ambulatory care visits are associated with a diagnosis of arthritis and other rheumatic conditions (AORC), or nearly 10% of all visits that year. Of these visits, OA makes up 22% of the total and joint pain a further 36%[44].

As a chronic condition with no cure, treatment for OA is ongoing. For the years 2008 to 2011, the mean per-person US total medical expenditures for OA and allied disorders was $11,029 [44]. Aggregate medical expenditures for the estimated 30.8 million persons with OA and allied disorders in the US averaged $340 billion in each of the years 2008 to 2011 [44].

Incremental medical expenditures, mean per-person earnings losses attributed to OA and allied disorders averaged $4,951 per year in 2008 to 2011[44]. Combining the direct and indirect costs for OA and allied disorders results in a total average cost of $461 billion, with incremental costs of $142 billion [44]

A recent study using US Medical Expenditure Panel Survey data for the years 1996 to 2005 found that OA-related out of pocket (OOP) costs incurred by women was greater than that by men. Having OA increased average OOP expenditure for women by $1,379 per year and insurer expenditure increased by $4,833. Among men, OA increased OOP expenditures by $694 per annum and insurer expenditures by $4,036. Overall, OA raised aggregate annual medical care expenditures by $185.5 billion. Of that amount, insurer expenditures were $149.4 billion and OOP expenditures were $36.1 billion [134].

More women than men were hospitalized for OA and those in older age groups were more likely to be hospitalized for OA than younger groups (**Figures 14-16**)

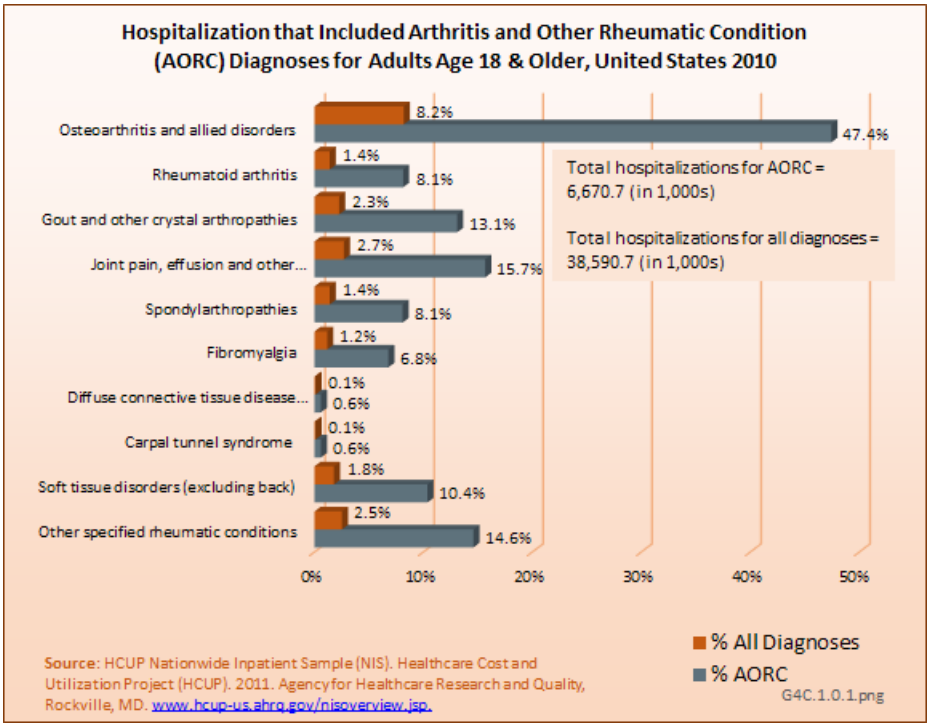


Figure 14

(BMUS website - http://www.boneandjointburden.org/2014-report/ivc10/hospitalization)

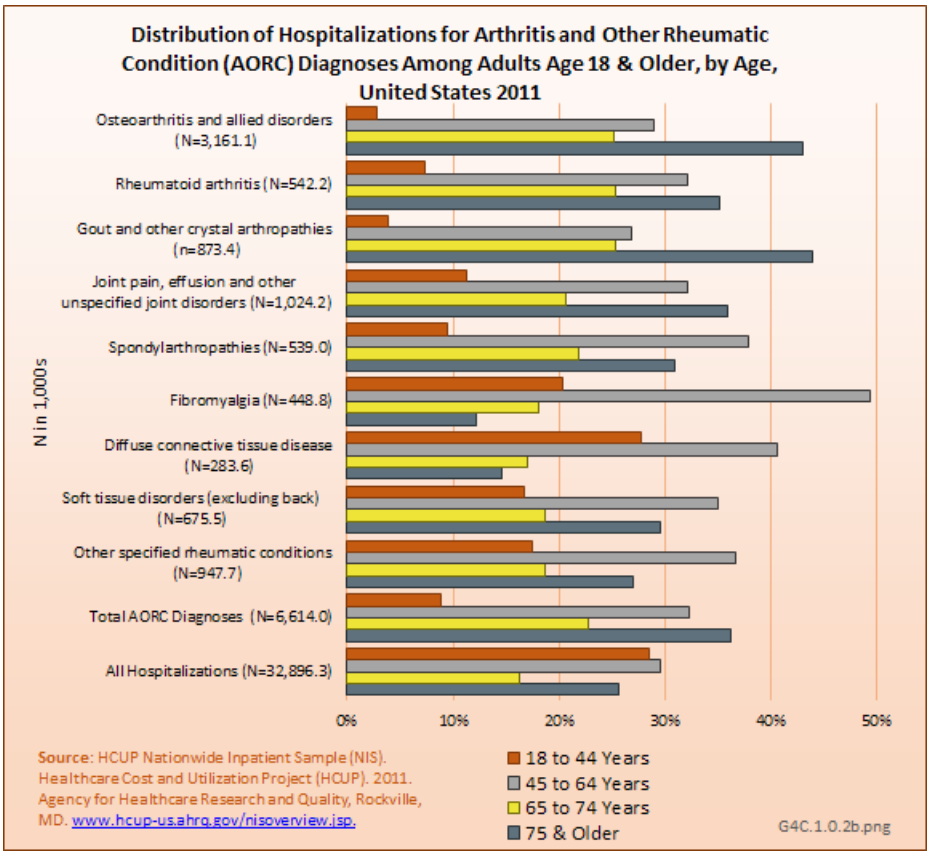


Figure 15: Hospitalizations by age
(BMUS website - http://www.boneandjointburden.org/2014-report/ivc10/hospitalization)

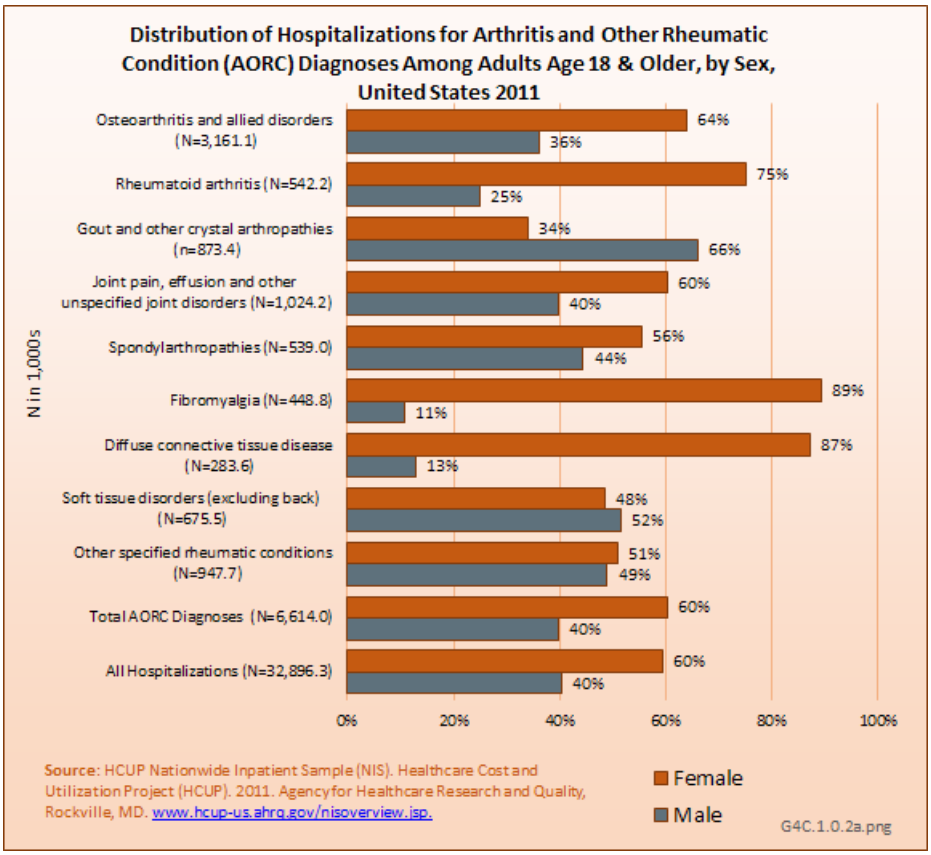


Figure 16: Hospitalizations by sex
(BMUS website - http://www.boneandjointburden.org/2014-report/ivc10/hospitalization)

DISEASE PROGRESSION IN OSTEOARTHRITIS

The assessment of the progression of OA over time is complicated by the variation in definitions of OA and OA progression. A meta-analysis of prognostic factors for radiographic progression found that baseline knee pain, presence of Heberden nodes, varus alignment, and high levels of serum markers hyaluronic acid and tumor necrosis factor-α predict knee OA progression [135]. Sex, knee injury, and quadriceps strength, among others, did not predict knee OA progression.

A systematic review assessing patient characteristics that predict the progression of knee OA found age, varus knee alignment, presence of OA in multiple joints, and radiographic features had strong evidence as predictors of knee OA progression [136]. Body mass index was a strong predictor for long-term progression (more than 3 years). Moderate participation in physical activity was not associated with progression. However, numerous other variables had limited or conflicting evidence as predictors of progression.

There is, however, no evidence for any agent consistently providing clinically and statistically significant slowing of progression of OA.

Data from the National Institutes of Health Osteoarthritis Initiative (OAI)[137] has been assessed to determine rates of progression of radiographic knee OA. The Kellgren Lawrence (KL) scale is often used to classify the degree of deterioration of the joint.

Kellgren-Lawrence grading scale for OA:

Grade 0: normal

Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping

Grade 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph

Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity

Grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

In **Table 10** below, incident radiographic OA is a person who was KL0/1 at baseline, and who is KL 2 or more by the 48 month follow-up. Progressive radiographic OA is anyone who was KL 2 or more at baseline, and who increased by 1 grade by the 48 month follow-up.

Table 10: Progression of OA knee according to Kellgren Lawrence scale

	KL 0 N = 1342	KL 1 = 688	KL 2 = 1173	KL 3 = 787	KL 4= 289
Incident ROA	53 (3.7%)	112 (16.3%)	-	-	-
Progressive ROA	-	-	135 (11.5%)	137 (17.4%)	-
TKR (in first 72 months of OAI)	3 (0.2%)	5 (0.7%)	33 (2.8%)	87 (11.1%)	95 (32.9%)

NB: These total numbers do not add up as data not available for all categories.

Data from the OAI were also assessed to determine the proportion of people with knee OA who progress to total knee replacement (TKR) according to levels of obesity, a significant risk factor for knee OA. **Tables 11 and 12** below demonstrate that progression to TKR over the 72 month period, increases with increasing BMI. With a BMI of 30+, 5.4% of males and 5.9% of females progress to TKR. Progression to TKR increases with both age and BMI.

Table 11: Rates to progression to TKR for BMI subgroups by gender

BMI	Males	Females
<20	0%	1.4%
20-25	2.9%	3.4%
25-30	4.9%	5.4%
30+	5.4%	5.9%

Table 12: Rates to progression to TKR for BMI subgroups by age

BMI	45-55	55-65	65-75	75+
<20	0%	0%	4.3%	0%
20-25	1.2%	4.0%	4.1%	5.1%
25-30	2.1%	5.3%	6.7%	10.1%
30+	3.5%	5.7%	8.2%	9%

THERE IS A LACK OF A CURE FOR OA

Currently OA is an incurable condition. Recent guidelines have addressed the many treatments that aim to relieve symptoms, in particular pain and improved function [18]. A recent systematic review of the effectiveness of pharmacologic interventions for knee OA assessed randomized trials of adults with knee OA comparing the common treatments including acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib, intra-articular (IA) corticosteroids, IA hyaluronic acid, oral placebo, and IA placebo[138].

Analysis of the data found that for pain reduction, all interventions were better than oral placebo, with effect sizes from 0.63 (95% credible interval [CrI], 0.39 to 0.88) for hyaluronic acid to 0.18 (CrI, 0.04 to 0.33) for acetaminophen. For function, all interventions except IA corticosteroids were significantly better than oral placebo. For stiffness, most of the treatments did not significantly differ from one another[138].

While this study shows that treatments may be effective for reducing pain, long-term data is lacking and safety data is inadequate. Again it should be noted that these treatments are for the reduction of symptoms, and do not provide a cure for OA. Treatments are needed that alter the natural history of increasing joint damage, and could possibly increase cartilage, decrease bone marrow lesions and robustly reduce inflammation associated with OA

ADVERSE EFFECTS OF CURRENTLY AVAILABLE OA TREATMENTS

The treatments that are available for the management of OA have adverse effects that are not insignificant. One of the more common treatments for OA is non-steroidal anti-inflammatory drugs. While these are effective in relieving pain there are a number of adverse effects.

NSAIDs have significant adverse events

Painful OA accounts for the majority of NSAID use, however NSAID use has been shown to increase the risk of serious conditions. It has been shown that six out of seven NSAIDs were associated with clinically relevant twofold to fourfold increases in the risk of myocardial infarction, stroke, or cardiovascular death compared with placebo [28]

NSAIDs increase the risk of:

- Peptic ulcer bleed and/or perforation
    - the risk of peptic ulcer bleeding was shown in meta-analysis to be increased by a factor of 4.85 with the use of NSAIDs[139]
    - compared to placebo, NSAID use increased hospitalization rates for gastrointestinal bleeding among Medicaid recipients over the age of 65 years (odds ratio 4.7)[139]
    - as many as 25% of chronic NSAID users will develop ulcer disease and 2–4% will bleed or perforate[139]
    - gastrointestinal hemorrhage, perforation and ulcer disease due to NSAIDs has been reported in more than 100,000 hospital admissions annually in the US and between 7,000 and 10,000 deaths, especially among those who have been designated as being in a high-risk category [139]
- Death from cardiovascular disease[28]
    - A systematic review reported that NSAIDS, except naproxen, showed some evidence for an increased risk of cardiovascular death compared with placebo. The estimated rate ratios for cardiovascular death were 2.39 for ibuprofen (95% credibility interval 0.69 to 8.64), 3.98 for diclofenac (1.48 to 12.70), celecoxib 2.07 (0.98 to 4.55), etoricoxib 4.07 (1.23 to 15.70), rofecoxib 1.58 (0.88 to 2.84), and lumiracoxib 1.89 (0.64 to 7.09).
- Atrial fibrillation [140]
    - NSAID use was associated with a 12% increased risk for AF incidence (RR 1.12, 95% CI 1.06 to 1.18). The association was found to be apparent for new users, with a 53% increase in risk.
- Chronic kidney disease [141]
    - NSAID use is associated with increased risk of chronic kidney disease in subjects with hypertension. The results showed that NSAID use was associated with a 1.18-fold increased risk of CKD in subjects taking NSAIDs for 1 to 89 days; and a 1.32-fold increased risk of CKD in hypertension subjects taking NSAIDs for >=90 days, compared with subjects not taking any NSAIDs.

Opioids are not more effective and may be more harmful

Opioids are another class of drugs that can be used to treat the pain associated with OA, however these also have considerable harmful effects. A review of studies of efficacy of opioids in patients with OA revealed that strong opioids were not more effective than NSAIDs and, in some studies, than placebo[28]. A meta-analysis of studies of opioids in OA showed that while there may be a small benefit in pain reduction from treatment with opioids, this

is outweighed by significant increases in risk of adverse events[142]. The use of opioids has been shown to raise the risk of all-cause mortality compared with use of NSAIDs [143].

There is also a high rate of mortality due to the misuse and abuse of strong opioids, accounting for approximately 10,000 deaths/year in the US[28].

Joint replacement surgery

Total joint replacement surgery (TJR) is a treatment for end-stage OA, and is not considered a cure as there are still limitations remaining post-surgery. More than one in ten people undergoing hip and knee replacement continue to experience pain in the replaced joint[144]

While post-operative mortality is low in healthy OA patients, the presence of comorbidities and functional limitations prior to sugery are associated with higher mortality[145]. A recent systematic review of mortality associated with TJR estimated the pooled incidence of mortality during the first 30 and 90 days following hip replacement to be 0.30% (95% CI 0.22 to 0.38) and 0.65% (95% CI 0.50 to 0.81), respectively [146]. Cardiovascular complications were the leading cause of death among these hip replacement patients.

Apart from mortality, longer term adverse events of TJR include infection, stiffness and loss of function as a result of scar tissue and other complications, and prosthesis problems.

Conclusions and Way Forward

There is clear evidence that there is a substantially increased risk of progressive disability in many patients diagnosed with OA and this progression is clearly associated with an increase in all cause mortality. The total number of OA patients is not fully recognized as the majority of the data has historically been derived from studies focusing on patients with hip and knee OA with limited analysis of patients impacted by OA of the hands, fingers and other joints.

The goal of this white paper was to demonstrate that many patients with OA clearly suffer from a serious disease, and the progressive disability observed in these patients is associated with reduced mobility and increased risk for death. Both of these findings fulfill the FDA definition of a serious disease. The evidence from numerous data analyses discussed within this white paper provides justification for the consideration of allowing the use of surrogate markers for the early approval of structure modifying drugs per subpart H and E of the Food and Drug Cosmetic Act. Allowing the use of surrogate markers during the drug approval process, which may be *reasonably likely* to predict important clinical outcomes, would increase the potential for the development of therapies for OA where currently there is no known cure and no interventions available to stop the progression or manage the symptoms (e.g., pain) with an acceptable benefit to harm profile. The use of surrogate outcomes to test potential structure modifying therapies would allow pharmaceutical companies to decrease the length of the clinical trials; however, companies would be required to commit to post approval linkage studies to prove the longitudinal benefit to harm profile and the durability of the potential new therapies. The linkage to acceptable meaningful clinical outcomes is critical. Current OA trials require both clinically relevant symptom improvement with concomitant structural improvement. These trials have been shown to fail,

likely due to the disassociation between the structural benefit, which might have a delayed demonstratable clinically relevant benefit.

With the global impact of OA constituting a major challenge for health systems in the twenty-first century and in the coming years, the importance of having therapies available to stop the disease progression and to manage the symptoms (e.g., pain) needs to be a priority. Confirming OA as a serious disease, whose progressive course and associated impairment and comorbidities are associated with an increase in mortality for numerous patients, is an important step for consideration of allowing the use of surrogate markers per subpart H and E of the Food and Drug Cosmetic Act in the development of structure modifying therapies.

OARSI White Paper Executive Committee

Francis Berenbaum, MD, PhD
Head, Department of Rheumatology
Faculty of Medicine Pierre & Marie Curie Paris VI
Saint-Antoine Hospital
Paris, France

Philip G. Conaghan, MBBS, PhD
Professor of Musculoskeletal Medicine
University of Leeds
Deputy Director, Leeds NIHR
Biomedical Research Unit
Leeds, UK

Marc C. Hochberg, MD, MPH
Professor of Medicine, Epidemiology and Public Health
Head, Division of Rheumatology and Clinical Immunology
Vice Chair, Department of Medicine
University of Maryland School of Medicine
Director, Medical Care Clinical Center
Baltimore VA Medical Center
Baltimore, MD

Virginia Byers Kraus, MD, PhD
Professor of Medicine
Division of Rheumatology, Duke University School of Medicine
Duke Molecular Physiology Institute
Durham, NC

Lee S. Simon, MD
Former Division Director, FDA Analgesic, Anti-inflammatory, Ophthalmologic Drug Products Division (CDER)
Principal SDG, LLC
Cambridge, MA

OARSI White Paper Writing Group

Lyn March, MBBS, MSc, PhD (Also served on Executive Committee)
Liggins Professor of Rheumatology and Musculodkeletal Epidemiology
Institute of Bone and Joint Research
University of Sydney
Senior Staff Specialist Rheumatologist
Royal North Shore Hospital
NSW, Australia

Marita Cross, BSc, MPH, PhD
Post Doctoral Fellow
Institute of Bone and Joint Research
University of Sydney
Sydney, NSW, Australia

Charmaine Lo, BMusStudies
MD Student
Sydney Medical School
University of Sydney
NSW, Australia

Nigel Arden, MBBS, MSc
Professor in Rheumatic Diseases and Consultant Rheumatologist
University of Southhampton, Southhampton University Hospitals NHS Trust
Reader in Musculoskeletal Sciences and Consultant Rheumatologist
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
Botnar Research Centre
University of Oxford, UK

Lucy Gates, BSc (hons), PhD
Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, University of Oxford, Oxford, UK
Faculty of Health Sciences, University of Southampton, Southampton, UK

Kirsten Leyland BA, MSc, PhD
Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis
University of Oxford, Oxford, UK

Gillian Hawker, MD (Also Served on Executive Committee)
Senior Scientist, Women's College Research Institute
Chair, Department of Medicine
Sir John and Lady Eaton Professor, Department of Medicine
Professor, Institute of Health Policy, Management and Evaluation
University of Toronto
Toronto, Canada

Lauren King MBBS MSc
Resident physician
Department of Medicine, University of Toronto

Reviewers
David Felson, MD
NIHR Manchester Musculoskeletal Biomedical Research Unit
University of Manchester, UK
Director, Clinical Epidemiology
Professor of Medicine and Public Health
Boston University School of Medicine
Boston, MA

Francis Guillemin, MD, PhD
Professor of Epidemiology and Public Health
School of Public Health, Faculty of Medicine
University of Nancy
France

Graeme Jones, MBBS, MMedSC
Professor of Rheumatology and Epidemiology
Head, Musculoskeletal Unit, Menzies Research Institute
University of Tasmania
Head of Department of Rheumatology, Royal Hobart Hospital
Hobart, TAX, Australia

Tore Kvien, MD, PhD
Professor of Rheumatology, University of Oslo
Head, Department of Rheumatology
Diakonhjemmet Hospital
Oslo, Norway

Michael Nevitt, PhD, MPH
Professor, University of California San Francisco School of Medicine
Department of Epidemiology and Biostatistics
San Francisco, CA

Alan Silman, MD, MSc
Professor of Musculoskeletal Health, Oxford University
Professor of Medicine, Keele University
UK

REFERENCES

1. Standardization of Osteoarthritis Definitions. (Accessed 17 December 2015, at http://oarsi.org/research/standardization-osteoarthritis-definitions.)
2. Osteoarthritis. 2015. (Accessed 13 December 2015, 2015, at http://www.cdc.gov/arthritis/basics/osteoarthritis.htm.)
3. World Health Organisation, Department of Health Statistics and Information Systems. WHO methods and data sosurces for global burden of disease estimates 2000-2011. Geneva; 2013.
4. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73:1323-30.
5. Vos T, et a. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800.
6. Hoy DG, Smith E, Cross M, et al. Reflecting on the global burden of musculoskeletal conditions: lessons learnt from the global burden of disease 2010 study and the next steps forward. Ann Rheum Dis 2015;74:4-7.
7. Yelin E, Murphy L, Cisternas M, Foreman A, Pasta D, Helmick C. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons to 1997. Arthritis and Rheumatism 2007;56:1397-407.
8. Murphy L, Helmick C. The impact of osteoarthritis in the United States: a population-health perspective. Am J Nurs 2012;112:S13-9.
9. Gabriel S, Crowson C, Campion M, et a. Direct medical costs unique to people with arthritis. J Rheumatol 1997;24:719–25.
10. Buckwalter J, Saltzman C, Brown T. The impact of osteoarthritis. Clin Orthoped Rel Res 2004;427S:S6-S15.
11. US Department of Health and Human Services, Food and Drug Administration. FDA. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. In: Services USDHHS, FDA, CDER, CBER. May 2014.
12. WHO Library Cataloguing-in-Publication Data. World report on ageing and health. 1. Aging. 2. Life Expectancy. 3. Aged. 4. Health Services for the Aged. 5. Global Health 6. Population Dynamics. 7. Delivery of Health Care. Geneva: World Health Organisation; 2015.
13. WHO Library Cataloguing-in-Publication Data. WHO global disability action plan 2014-2021. Better health for all people with disability. Geneva: World Health Organisation; 2015.
14. Briggs AM, Cross MJ, Hoy DG, et al. Musculoskeletal health conditions represent a global threat to healthy ageing: A report for the World Health Organisation World Report on Ageing and Health. The Gerontologist In press.
15. Hootman J, Murphy L, Helmick C, Barbour K. Arthritis as a potential barrier to physical activity among adults with obesity—United States, 2007 and 2009. MMWR Morbidity and mortality weekly report 2011;60:614–8.
16. Bolen J, Murphy L, Greenlund K, et al. Arthritis as a potential barrier to physical activity among adults with heart disease - United States, 2005 and 2007. MMWR Morbidity and mortality weekly report 2009;58:165–9.
17. Bolen J, Hootman J, Helmick C, Murphy L, Langmaid G, Caspersen C. Arthritis as a potential barrier to physical activity among adults with diabetes - United States, 2005 and 2007. MMWR Morbidity and mortality weekly report 2008;57:486–9.
18. McAlindon T, Bannuru R, Sullivan M, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage 2014;22:363-88.
19. Speerin R, et a. Moving from evidence to practice: Models of care for the prevention and management of musculoskeletal conditions. Best Practice & Research Clinical Rheumatology 2014;28:479-515.
20. Parmelee P, Harralson T, McPherron J, DeCoster J, Schumacher H. Pain, disability, and depression in osteoarthritis: effects of race and sex. J Aging Health 2012;24:168-87.
21. Keefea FJ, Lefebvrea JC, Egertb JR, Affleckc G, Sullivand MJ, Caldwella DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 2000;87:325–34.
22. Badley E, Ibañez D. Socioeconomic risk factors and musculoskeletal disability. J Rheumatol 1994;21:515-22.

23. Kaplan R, Alcaraz J, Anderson J, Weisman M. Quality-adjusted life years lost to arthritis: effects of gender, race, and social class. Arthritis Care Res 1996;9:473–82.
24. Holte HH, Tambs K, Bjerkedal T. Manual work as predictor for disability pensioning with osteoarthritis among the employed in Norway 1971–1990 International Journal of Epidemiology 2000;29:487–94.
25. Stebbings S, Herbison P, Doyle T, Treharne G, Highton J. A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: disparity in associations with disability, anxiety and sleep disturbance. Rheumatology 2010;49:361-7.
26. March LM, Cross MJ, Lapsley H, et a. Outcomes after hip or knee replacement surgery for osteoarthritis. A prospective cohort study comparing patients' quality of life before and after surgery with age-related population norms. Med J Aust 1999;171:235-8.
27. Jones CA, Beaupre LA, Johnston DWC, Suarez-Almazor ME. Total Joint Arthroplasties: Current Concepts of Patient Outcomes after Surgery. Rheum Dis Clin N Am 2007;33:71-86.
28. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.
29. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. The Lancet 2013;382:769–79.
30. Chronic rheumatic conditions. (Accessed 13 December, 2015, at http://www.who.int/chp/topics/rheumatic/en/.)
31. Hootman JM, Helmick CG. Projections of U.S. prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006;54:226–9.
32. King L, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res 2013;138:185–93.
33. Obesity and overweight WHO Fact Sheet No. 311. 2015. (Accessed 13 December, 2015, at http://www.who.int/mediacentre/factsheets/fs311/en/.)
34. Dekkera J, van Dijkc GM, Veenhofc C. Risk factors for functional decline in osteoarthritis of the hip or knee. Current Opinion in Rheumatology 2009;21:520–4.
35. Physical Activity. WHO Fact Sheet No 385. 2015. (Accessed 13 December, 2015, at http://www.who.int/mediacentre/factsheets/fs385/en/.)
36. Roos E. Joint injury causes knee osteoarthritis in young adults. Current Opinion in Rheumatology 2005;17:195–200.
37. Gage B, McIlvain N, Collins C, Fields S, Comstock R. Epidemiology of 6.6 million knee injuries presenting to United States emergency departments from 1999 through 2008. Academic Emergency Medicine 2012;19:378–85.
38. GBD Compare. 2015. (Accessed 13 December 2015, at http://vizhub.healthdata.org/gbd-compare/.)
39. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2013;380:2163-96.
40. Arden N, et al. Knee pain, knee arthritis and risk of fracture. Arthritis Care & Research 2006;55:610-5.
41. Guillemin F, Rat A, Roux C, et al. The KHOALA cohort of knee and hip osteoarthritis in France. Joint Bone Spine 2012;79:597-603.
42. Hawker G, Stewart L, French M, et al. Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008;16:415–22.
43. Guccione AA, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Pub Health 1994;84:351–8.
44. The Burden of Musculoskeletal Diseases in the United States (BMUS), Third Edition. 2014. (Accessed 13 December 2015, at http://www.boneandjointburden.org.)
45. Price K, Taylor A, Carrangis N, Pilkington R, Kralik D, Eaton H. People with chronic diseases and the influence of trial and error practices as a self-care strategy: a novel approach: Report 1b–Socio-demographic and clinical profile of people aged 65 years and older with arthritis, compared to people age 65 years and over with no chronic conditions. Adelaide: University of South Australia; 2009.
46. Losina E, Walensky RP, Reichmann WM, et al. Impact of obesity and knee osteoarthritis on morbidity and mortality in older americans. Ann Intern Med 2011;154:217–26.
47. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nature Reviews Rheumatology 2014;10:437–41.

48. van der Waal J, Terwee C, van der Windt D, Bouter L, Dekke J. The impact of non-traumatic hip and knee disorders on health-related quality of life as measured with the SF-36 or SF-12. A systematic review. Quality of Life Research 2005;14:1141–55.
49. Smith T, Purdy R, Lister S, Salter C, Fleetcroft R, Conaghan P. Living with osteoarthritis: a systematic review and meta-ethnography. Scand J Rheumatol 2014;43:441–52.
50. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. Ann Rheum Dis 2011;70:921–8.
51. Nelson A, Smith M, Golightly Y, Jordan J. "Generalized osteoarthritis": a systematic review. Seminars in Arthritis & Rheumatism 2014;43:713-20.
52. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among US adults: a 2012 update. Preventing chronic disease 2014;11:E62.
53. Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JT, van Weel C. Comorbidity of chronic diseases in general practice. Journal of clinical epidemiology 1993;46:469-73.
54. Hawker GA, Croxford R, Bierman AS, et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: A population based cohort study. PLoS ONE 2014;9:e91286.
55. Haugen IK, Ramachandran VS, Misra D, et al. Hand osteoarthritis in relation to mortality and incidence of cardiovascular disease: data from the Framingham Heart Study. Ann Rheum Dis 2015;74:74–81.
56. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ (Clinical research ed) 2011;342:d1165.
57. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Annals of the rheumatic diseases 2004;63:408-14.
58. Ayers DC, Franklin PD, Ploutz-Snyder R, Boisvert CB. Total knee replacement outcome and coexisting physical and emotional illness. Clinical orthopaedics and related research 2005;440:157-61.
59. van Dijk GM, Veenhof C, Schellevis F, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC musculoskeletal disorders 2008;9:95.
60. Caporali R, Cimmino MA, Sarzi-Puttini P, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug prescriptions by general practitioners and specialists. Seminars in arthritis and rheumatism 2005;35:31-7.
61. Juhakoski R, Tenhonen S, Anttonen T, Kauppinen T, Arokoski JP. Factors affecting self-reported pain and physical function in patients with hip osteoarthritis. Archives of physical medicine and rehabilitation 2008;89:1066-73.
62. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2013;21:1648-59.
63. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? Clinical rheumatology 2010;29:739-47.
64. van Dijk GM, Veenhof C, Spreeuwenberg P, et al. Prognosis of limitations in activities in osteoarthritis of the hip or knee: a 3-year cohort study. Archives of physical medicine and rehabilitation 2010;91:58-66.
65. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
66. Calvet J, Orellana C, Larrosa M, et al. High prevalence of cardiovascular co-morbidities in patients with symptomatic knee or hand osteoarthritis. Scandinavian journal of rheumatology 2015:1-4.
67. Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. BMJ open 2013;3.
68. Hunter DJ, Felson DT. Osteoarthritis. BMJ (Clinical research ed) 2006;332:639-42.
69. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 2010;122:743-52.
70. Li TY, Rana JS, Manson JE, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation 2006;113:499-506.
71. Ravi B, Croxford R, Austin PC, et al. The relation between total joint arthroplasty and risk for serious cardiovascular events in patients with moderate-severe osteoarthritis: propensity score matched landmark analysis. BMJ (Clinical research ed) 2013;347:f6187.

72. Lin WY, Lee CC, Hsu CW, Huang KY, Lyu SR. Patients with knee osteoarthritis undergoing total knee arthroplasty have a lower risk of subsequent severe cardiovascular events: propensity score and instrumental variable analysis. PloS one 2015;10:e0127454.
73. Prior JA, Jordan KP, Kadam UT. Associations between cardiovascular disease severity, osteoarthritis co-morbidity and physical health: a population-based study. Rheumatology (Oxford, England) 2014;53:1794-802.
74. Rushton CA, Kadam UT. Impact of non-cardiovascular disease comorbidity on cardiovascular disease symptom severity: a population-based study. International journal of cardiology 2014;175:154-61.
75. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet (London, England) 2007;369:750-6.
76. Beckles GL, Chou CF. Diabetes - United States, 2006 and 2010. Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002) 2013;62 Suppl 3:99-104.
77. Tuominen U, Blom M, Hirvonen J, et al. The effect of co-morbidities on health-related quality of life in patients placed on the waiting list for total joint replacement. Health and quality of life outcomes 2007;5:16.
78. Rahman MM, Cibere J, Anis AH, Goldsmith CH, Kopec JA. Risk of Type 2 Diabetes among Osteoarthritis Patients in a Prospective Longitudinal Study. International journal of rheumatology 2014;2014:620920.
79. Piva SR, Susko AM, Khoja SS, Josbeno DA, Fitzgerald GK, Toledo FG. Links between osteoarthritis and diabetes: implications for management from a physical activity perspective. Clinics in geriatric medicine 2015;31:67-87, viii.
80. Hawker G, Croxford R, Bierman A, et al. Osteoarthritis-related difficulty walking and risk for diabetes complications. Osteoarthritis and Cartilage 2016;In Press.
81. Gad BV, Higuera CA, Klika AK, Elsharkawy KA, Barsoum WK. Validity of patient-reported comorbidities before total knee and hip arthroplasty in patients older than 65 years. The Journal of arthroplasty 2012;27:1750-6.e1.
82. Gore M, Tai KS, Sadosky A, Leslie D, Stacey BR. Clinical comorbidities, treatment patterns, and direct medical costs of patients with osteoarthritis in usual care: a retrospective claims database analysis. Journal of medical economics 2011;14:497-507.
83. Nielen MM, van Sijl AM, Peters MJ, Verheij RA, Schellevis FG, Nurmohamed MT. Cardiovascular disease prevalence in patients with inflammatory arthritis, diabetes mellitus and osteoarthritis: a cross-sectional study in primary care. BMC musculoskeletal disorders 2012;13:150.
84. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgraduate medicine 2009;121:9-20.
85. Boeckxstaens P, Peersman W, Goubin G, et al. A practice-based analysis of combinations of diseases in patients aged 65 or older in primary care. BMC Family Practice 2014;15:159.
86. Aljadhey H, Tu W, Hansen RA, Blalock SJ, Brater DC, Murray MD. Comparative effects of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure in patients with hypertension. BMC cardiovascular disorders 2012;12:93.
87. Hsu CC, Wang H, Hsu YH, et al. Use of Nonsteroidal Anti-Inflammatory Drugs and Risk of Chronic Kidney Disease in Subjects With Hypertension: Nationwide Longitudinal Cohort Study. Hypertension (Dallas, Tex : 1979) 2015;66:524-33.
88. Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiology in review 2011;19:184-91.
89. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. Jama 2014;311:806-14.
90. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898-918.
91. Pratt LA, Brody DJ. Depression in the U.S. household population, 2009-2012. NCHS data brief 2014:1-8.
92. Leite AA, Costa AJ, Lima Bde A, Padilha AV, Albuquerque EC, Marques CD. Comorbidities in patients with osteoarthritis: frequency and impact on pain and physical function. Revista brasileira de reumatologia 2011;51:118-23.
93. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Archives of internal medicine 2003;163:2433-45.

94. White DK, Tudor-Locke C, Zhang Y, et al. Prospective change in daily walking over 2 years in older adults with or at risk of knee osteoarthritis: the MOST study. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2015.
95. Lin EH. Depression and osteoarthritis. The American journal of medicine 2008;121:S16-9.
96. Bergen G, Stevens MR, Burns ER. Falls and Fall Injuries Among Adults Aged >/=65 Years - United States, 2014. MMWR Morbidity and mortality weekly report 2016;65:993-8.
97. Cevei MI, Stoicanescu D, Nemes D. Osteoarticular comorbidities in hip osteoarthritis. Annals of the Rheumatic Disease;Conference:Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2012 Berlin Germany.
98. Choi EJ, Kim SA, Kim NR, Rhee J-A, Yun Y-W, Shin M-H. Risk factors for falls in older Korean adults: the 2011 Community Health Survey.[Erratum appears in J Korean Med Sci. 2015 Jan;30(1):117; PMID: 25547180]. Journal of Korean Medical Science 2014;29:1482-7.
99. Barbour KE, Stevens JA, Helmick CG, et al. Falls and fall injuries among adults with arthritis--United States, 2012. MMWR Morbidity and mortality weekly report 2014;63:379-83.
100. Hochberg MC. Mortality in osteoarthritis. Clin Exp Rheumatol 2008;26:S120-S4.
101. Cerhan J, Wallace R, El-Khoury G, Moore T, Long C. Decreased survival with increasing prevalence of full-body, radiographically defined osteoarthritis in women. Am J Epidemiol 1995;141:225-34.
102. Watson D, Rhodes T, Guess H. Allcause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30:1196-202.
103. Haara M, Manninen P, Kroger H, et a. Osteoarthritis of finger joints in Finns aged 30 and over: prevalence, determinants, and association with mortality. Ann Rheum Dis 2003;62:151-8.
104. Kumar N, Marshall NJ, Hammal DM, et al. Causes of death in patients with rheumatoid arthritis: Comparison with siblings and matched osteoarthritis controls. J Rheumatol 2007;34:1695–8.
105. Tsuboi M, Hasegawa Y, Matsuyama Y, Suzuki S, Suzuki K, Imagama S. Do musculoskeletal degenerative diseases affect mortality and cause of death after 10 years in Japan? J Bone Miner Metab 2011;29:217–23.
106. Cacciatore F, Della-Morte D, Basile C, et al. Long-term mortality in frail elderly subjects with osteoarthritis. Rheumatology ;: 2014;53:293-9.
107. Liu R, Kwok W, Vliet Vlieland T, et al. Mortality in osteoarthritis patients. Scand J Rheumatol 2015;44:70–3.
108. Barbour K, Lui L, Nevitt M, et al. Hip Osteoarthritis and the Risk of All-Cause and Disease-Specific Mortality in Older Women: A Population-Based Cohort Study. Arthritis Rheumatol 2015;67:1798-805.
109. Liu Q, Niu J, Huang J, et al. Knee osteoarthritis and all-cause mortality: the Wuchuan Osteoarthritis Study. Osteoarthritis and Cartilage 2015;23:1154-7.
110. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study — A large observational study of the determinants of fracture in older men. Contemporary Clinical Trials 2005;26:569-85.
111. Kang X, Fransen M, Zhang Y, et al. The high prevalence of knee osteoarthritis in a rural Chinese population: The Wuchuan osteoarthritis study. Arthritis Care & Research 2009;61:641-7.
112. Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing osteoarthritis study. Arthritis & Rheumatism 2001;44:2065-71.
113. Verbrugge LM, Gruber-Baldini AL, Fozard JL. Age Differences and Age Changes in Activities: Baltimore Longitudinal Study of Aging. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 1996;51B:S30-S41.
114. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The framingham offspring study. Design and preliminary data. Preventive Medicine 1975;4:518-25.
115. Jordan J, M., Linder G, F., Renner J, B., Fryer J, G. The Impact of Arthritis in Rural Populations. Arthritis Care and Research 1995;8:242-50.
116. Cummings SR, Black DM, Nevitt MC, et al. APpendicular bone density and age predict hip fracture in women. Jama 1990;263:665-8.
117. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheumatic Disease Clinics of North America 2004;30:783-97.
118. Hart DJ, Mootoosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford Study. Ann Rheum Dis 1994;53:158-62.
119. Syddall H, Aihie Sayer A, Dennison E, et al. Cohort Profile: The Hertfordshire Cohort Study. International Journal of Epidemiology 2005;34:1234-42.

120. Hofman A, Murad SD, Duijn CM, et al. The Rotterdam Study: 2014 objectives and design update. European Journal of Epidemiology 2013;28:889-926.
121. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort Profile: Research on Osteoarthritis/Osteoporosis Against Disability study. International Journal of Epidemiology 2010;39:988-95.
122. Ding C, Parameswaran V, Cicuttini F, et al. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis 2008;67:1256-61.
123. Agaliotis M, Mackey MG, Jan S, Fransen M. Burden of reduced work productivity among people with chronic knee pain: a systematic review. Occup Environ Med 2014;71:651–9.
124. Sayre E, Li L, Kopec J, et a. The effect of disease site (knee, hip, hand, foot, lower back or neck) on employment reduction due to osteoarthritis. PLoS ONE 2010;5:e10470.
125. Fautrel B, Hilliquin P, Rozenberg S, et a. Impact of osteoarthritis: results of a nationwide survey of 10,000 patients consulting for OA. Joint Bone Spine 2005;72:235–40.
126. Leardini G, Salaffi F, Caporali R, et a. Direct and indirect costs of osteoarthritis of the knee. Clin Exp Rheumatol 2004;22:699–706.
127. Hubertsson J, Petersson IF, Thorstensson C, et a. Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. Ann Rheum Dis 2013;72:401–5.
128. Woo J, Lau E, Lau C, et a. Socioeconomic impact of osteoarthritis in Hong Kong: utilization of health and social services, and direct and indirect costs. Arthritis Rheum 2003;49:526–34.
129. Hutchings A, Calloway M, Choy E, et a. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. J Rheumatol 2007;34:2291–300.
130. Alexopoulos E, Tanagra D, Detorakis I, et a. Knee and low back complaints in professional hospital nurses: occurrence, chronicity, care seeking and absenteeism. Work 2011;38:329–35.
131. Makela M, Heliovaara M, Sievers K, et a. Musculoskeletal disorders as determinants of disability in Finns aged 30 years or more. J Clin Epidemiol 1993;46:549–59.
132. Zhang W, Gignac MA, Beaton D, Tang K, Anis AH. Productivity loss due to presenteeism among patients with arthritis: estimates from 4 instruments. J Rheumatol 2010;37:1805–14.
133. Schofield DJ, Shrestha RN, Percival R, Passey ME, Callander EJ, Kelly SJ. The personal and national costs of lost labour force participation due to arthritis: an economic study. BMC Public Health 2013;13:188.
134. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: Evidence from national survey data. Arthritis Rheum 2009;60:3546–53.
135. Bastick A, Belo J, Runhaar J, Bierma-Zeinstra S. What Are the Prognostic Factors for Radiographic Progression of Knee Osteoarthritis? A Meta-analysis. Clin Orthop Relat Res 2015;473:2969-89.
136. Chapple C, Nicholson H, Baxter G, Abbott J. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care & Research 2011;63:1115-25.
137. University of California, San Francisico. (Accessed 17 March, 2016, at https://oai.epi-ucsf.org/datarelease/Publications.asp.)
138. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: A systematic review and network meta-analysis Ann Intern Med 2015;162:46-54.
139. Lanza FL, Chan FK, Quigley EM. Prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728–38.
140. Liu G, Yan Y, Zheng X, et al. Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of atrial fibrillation. Am J Cardiol 2014 114:1523-9.
141. Hsu C, Wang H, Hsu Y, et al. Use of nonsteroidal anti-inflammatory drugs and risk of chronic kidney disease in subjects with hypertension: Nationwide longitudinal cohort study. Hypertension 2015;66:524-33.
142. daCosta B, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2014;9.
143. Solomon DH, Rassen J, Glynn R, Lee J, Levin R, Schneeweiss S. The Comparative Safety of Analgesics in Older Adults With Arthritis. Arch Intern Med 2010;170:1968-78.
144. Gwilym S, Pollard T, Carr A. Understanding pain in osteoarthritis. J Bone Joint Surg 2008;90-B:280-7.
145. Jämsen E, Puolakka T, Eskelinen A, et al. Predictors of mortality following primary hip and knee replacement in the aged. Acta Orthopaedica 2013;84:44–53.

146. Berstock J, Beswick A, Lenguerrand E, Whitehouse M, Blom A. Mortality after total hip replacement surgery: A systematic review. Bone Joint Res 2014;3:175–82.

Appendix 1

White Paper: Osteoarthritis and Mortality IPD Meta-analysis

Authors: Leyland, K.M.[1], Gates, L.S.[1,2], Sanchez-Santos, M.T.[1], Prieto Alhambra, D.[1], Judge, A.[1], Collins, G.[1] Cleveland, R.[3], Felson, D.[4], Jordan, J.M.[3], Callahan, L.F.[3], Nevitt, M.[5], Saberi Hosnijeh, F[6]. van Meurs, J.B.J. [6], Yoshimura, N.[7], Jones, G.[8], Altman, D. [1], Cooper, C. [1,2], Arden, N. [1,2]

[1]NIHR Musculoskeletal Biomedical Research Unit and Arthritis Research UK Centre for Sport, Exercise, and Osteoarthritis, University of Oxford, Oxford, UK

[2] University of Southampton, Southampton, UK

[3]University of North Carolina at Chapel Hill, Chapel Hill, NC USA

[4]Boston University School of Medicine, Boston, MA, USA

[5]University of California, San Francisco, CA, USA

[6]Erasmus University Medical Centre, Rotterdam, the Netherlands

[7]Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[8] Menzies Institute for Medical Research, University of Tasmania, Australia

1. INTRODUCTION

The rising prevalence rates and global impact of osteoarthritis has been shown in previous sections of this document, however the effect of osteoarthritis on the risk of mortality is less understood. A systematic review by Hochberg (1) has shown evidence of increased mortality among persons with osteoarthritis compared with the general population. A number of international studies have since confirmed this association in countries including the UK (2), Canada (3), the US (4) and China (5).

An individual patient level (IPD) meta-analysis utilises original raw data from cohorts and uses standardised statistical methods to analyse and produce pooled estimates. Traditional meta-analyses are valuable and efficient in terms of time and resources required but suffer from several limitations. They are limited to published data and may therefore suffer from publication biases as negative studies are often difficult to publish. Secondly most studies will vary in their definitions of exposures, confounders and outcomes, which may add to bias. IDP meta-analysis although time consuming and resource intensive, is not dependent on

previously published data allows for a standardised definition of symptomatic radiographic OA (SROA) and can be analysed using consistent statistical methods.

2. METHODS

Aim: To perform a two-stage IPD meta-analysis of all available population based cohorts to assess whether patients with OA of the hip and knee have an increased risk of premature mortality.

2.1. Study Design

This study was designed to look at the relationship between lower-limb osteoarthritis and all-cause mortality in multiple, prospective, longitudinal, population-based cohort studies from around the world. Subjects were stratified by the presence or absence of osteoarthritis at baseline and time-to-mortality was compared between groups.

2.2. Cohort selection

Cohort studies were identified by a literature review for established longitudinal osteoarthritis cohorts in the normal population in addition to expert knowledge of available data. Cohorts were selected based on the presence of appropriate pain and radiographic data at baseline. Thirty-three were identified as meeting this criteria and further searches and follow up liaison was conducted to establish the presence of available mortality data for these subjects. Cohorts were *not* selected for whether or not they had already published data on the relationship between OA and mortality. Nine cohorts were identified with data that had pain and radiographic data and were available for analysis (Johnston County, US; SOF, US; MOST, US; Framingham Offspring, US; Chingford, UK, Hertfordshire, UK; ROAD, Japan; Rotterdam, Netherlands; TasOAC, Australia). Four further cohorts were identified as having both OA and mortality data, but require further investigation of the usability of raw data (Osteoporotic Fractures in Men (MrOS) (6), Wuchuan OA study (7), Health ABC (8), Baltimore Longitudinal Study of Aging (9). Inclusion of these cohorts in future analyses would be beneficial to widen the global scope of this research. A detailed flow chart of cohort selection can be found in **appendix 1.** Several cohorts ultimately did not have the required detail for categorical OA of the hips and/or knees and are therefore presented in the analysis using pain alone or as non-side specific SROA.

The characteristics of the nine cohorts included in this analysis are described below in **table 1**. There are three normal population cohorts (Framingham, Johnston County Cohort, and Study of Osteoporotic Fractures (SOF)) (10-12) and one enhanced risk factor cohort (Multicentre Osteoarthritis Study (MOST) from the United States (13); two population-based cohorts from the United Kingdom (Chingford and Hertfordshire) (14,15); a Dutch population-based cohort (Rotterdam) (16); a Japanese population-based cohort (Research on Osteoarthritis/Osteoporosis Against Disability (ROAD)) (17); and an Australian population-based cohort (The Tasmanian Older Adult Cohort (TasOAC)) (18). The majority of cohorts had time-to-event data available for this analysis. The ROAD study had binary mortality event data collected at their year seven follow-up visit and will therefore be presented separately from studies containing time-to-event data. Pooled estimates will be produced for TasOAC and Rotterdam studies separately from the other non-US cohorts, due to a lack of side-specific pain data. The other key differences between cohorts are the year of baseline visit, length of follow-up and the age of participants at baseline.

Table 1. Cohort characteristics of the included cohorts

Cohort	Country	Year of Cohort Baseline	Original N	% of Women	Baseline Age	Follow-up (years)	Mortality
Chingford	UK	1989	1003	100%	44-67	23	Time-to-event
Hertfordshire	UK	1998	1412	50%	64.9 (2.7)	11	Time-to-event
Rotterdam	Netherlands	1997-99	7983	60%	>55	18	Time-to-event
Johnston County	USA	1991-97	4197	50%	61.1 (10.6)	23	Time-to-event
SOF	USA	1986-88	10000	100%	>65	23	Time-to-event
Framingham	USA	1971-75	5124	50%	55	14	Time-to-event
MOST	USA	2003	3026	60%	62	7	Time-to-event

TasOAC	Australia	2002-04	1099	50%	63.0 (7.5)	14	Time-to-event
ROAD	Japan	2005-07	3040	50%	70.2 (11.1)	7	Binary

2.3. Risk Factors, Confounders and Outcomes

Due to the importance of harmonising definitions of osteoarthritis, confounders and statistical methodology for IPD meta-analysis, we undertook a series of international consensus studies to gain expert agreement on the methods of harmonisation. A more detailed description of individual variables from each cohort can be seen in **appendix 2**.

2.3.1. Primary Risk Factor – Osteoarthritis

2.3.1.1. Radiographic Osteoarthritis

Comparing and pooling results between prospective cohort studies is relatively rare in the disease area of osteoarthritis, therefore an expert consensus meeting was convened to determine the best way to 'diagnose' osteoarthritis in the general population as well as harmonise this variable between cohort studies. Experts were drawn from around the world with a variety of backgrounds (**appendix 3**). The key output from this meeting was the decision to define OA using both self-reported pain and the presence of radiographic OA. Radiographic OA would be established using the validated scoring method of Kellgren and Lawrence (K/L), defined as a grade 2 or above (19).

If K/L grades were not available in the cohort, an equivalent combination of radiographic features (osteophytes and joint space narrowing) from other validated scoring methods (such as the OARSI atlas) (20) would be used to define the presence of ROA.

2.3.1.2. Pain

Pain would be defined by using either an NHANES-type question (i.e. 'have you had pain for at least a month in the last month in your joint') (21)or the WOMAC pain subscale (22) or alternative pain question (JoCo) if an NHANES-type question had not been used to assess pain. Due to the known variations in the wording of pain questions (23), further analysis was recommended by the experts to determine the most comparable wording of questions and to establish an equivalent threshold to use in the WOMAC pain sub-scale to create a binary pain

variable. The results of this analysis have been reviewed by all experts on the committee and will be presented at the 2016 Osteoarthritis Research International conference (OARSI) (**appendix 4**). All recommendations from the expert committee have been used to define OA in this analysis. Subjects were labelled as having OA if they had both pain and radiographic OA on the same side in the same joint, unless otherwise indicated.

Subsequent to the expert consensus meeting, a study on osteoarthritis and mortality in the Chingford cohort was published (24), which emphasised the necessity not to combine subjects who only had pain without radiographic osteoarthritis into the control group. The study found that subjects with ROA only had no increased risk of all-cause mortality, subjects with pain only and no ROA had a 49% increased risk (HR 1.49 95% CI 1.04 to 2.14; p=0.029) and that subjects with both pain and ROA had an increased risk reaching 97% (HR 1.97 95% CI 1.23 to 3.17; p=0.005) compared to subjects without pain and without ROA. Therefore, for this analysis, in cohorts with a large enough sample size, subjects were divided into four categories: **1** No OA; **2** asymptomatic ROA; **3** symptomatic OA (no ROA); **4** symptomatic ROA. Hips and knees were analysed separately. Person-level OA was calculated by assessing the OA status for each joint and using the 'highest' level of OA based on this system. For example, if a subject had no OA in their right knee and ROA in their left knee, their person-level knee OA status would be ROA.

A pain only analysis (regardless of ROA status) was used for cohorts if they were either missing radiographic OA data, if radiographic data was only available for paired x-rays, or if x-rays were based on a radiographic selection criteria that may bias results compared to other cohort selection criteria.

2.3.2. Outcome – Mortality

Mortality and follow-up data for all cohorts (except for ROAD) was linked to all subjects present at the baseline visit who also had a known follow up status (dead/alive/censored). Three cohorts (Chingford, Hertfordshire, TasOAC) determined the date of death using nationally linked records, while the remaining cohorts used other methods to determine the date of death such as updates from GP systems, death registries or municipal administration, family, medical records and periodic examinations or contacts (Framingham, Rotterdam, MOST, SOF and ROAD).

In cohorts where subjects were lost to follow-up at an unknown date, the previous visit where subjects had data was used as the last date where the subject's mortality status was known. Time-to-status was calculated from the baseline visit, determined by when OA was assessed, to the last date that the subject's status was known. Survival was calculated using person-years attributing to the analysis.

2.3.3. Confounders

Age was defined as age at the time of the clinic visit to assess baseline OA, in all cohorts. Chingford, Hertfordshire, SOF, TasOAC and Framingham have predominantly Caucasian subjects; Johnston County and MOST have both Caucasian and African American subjects; and ROAD has predominantly Japanese subjects. Race was included in the multivariable model for any cohort which had more than one race category reported. The Rotterdam cohort was not adjusted for race, as there was no equivalent self-reported race variable available.

Sex and race were only included in the fully adjusted model only when relevant to the specific cohort, for example, Chingford which is all women and predominantly Caucasian would only be adjusted for age in the full multivariable model.

2.4. Statistical Analysis

2.4.1. Inclusion Criteria and Missing Data

Complete case analysis was used due to the low number of missing observations within the main risk factor (osteoarthritis) (~15%) for all cohorts. Inclusion criteria were for subjects to have mortality data, be free from rheumatoid osteoarthritis at baseline and to be between the ages of 45 and 80 years. Subjects were then included in the analysis if they had data available to generate both the primary risk factor (osteoarthritis) and were not missing observations from any confounders (age, sex, race) (**table 2**). The baseline demographics for subjects included and excluded from the analysis were compared using t-tests (or Wilcoxon Man Whitney) for continuous variables and Chi^2 (Fishers exact) tests for categorical and binary variables (**appendix 5 & 6**).

Table 2. Subject Inclusion criteria and selection of complete cases

Cohort	Johnston County		Herts		ROAD		Framingham		MOST		SOF		Chingford		Rotterdam		TasOAC	
	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips
Original cohort n	**4197**	**4197**	**1412**		**3040**		**1166**		**3026**		**9704**	**862**			**7,983**	**7,983**	**1,100**	**1,100**
Subjects meeting Inclusion Criteria*	**3918**	**3918**	**957**		**2376**		**905**		**2936**		**8120**	**857**			**3,848**	**3,848**	**445**	**445**
Subjects without missing data**	**3762**	**3845**	**817**		**2354**		**886**		**2906**		**8055**	**683**			**2,813**	**3,795**	**410**	**439**

*Subjects without RA at baseline, aged between 45-80 years and with mortality data

**Subjects with Osteoarthritis, age, sex and race (where applicable) data

2.4.2. Regression Analysis

2.4.2.1. Survival Analysis (time-to-event outcome)

The association between OA and the time to all-cause mortality was assessed using Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95 percent confidence intervals (95% CIs). The univariable model assessed OA alone, with the multivariable models also adjusted for age, sex and race, where relevant. Linearity between age and mortality was assessed in all cohorts, and the proportional hazards assumption of the primary risk factor (OA) was tested using Schoenfeld residuals. There was no evidence that OA was not proportional with mortality during follow-up in any of the cohorts.

Kaplan-Meier survival curves were calculated for all categories of OA with all-cause mortality. An a priori interaction of OA and age was tested for in all cohorts.

2.4.2.2. Logistic Regression (binary outcome)

For cohorts without time-to-event data (ROAD), logistic regression models were used with categorical OA as the primary predictor and a binary outcome (death: yes/no). Linearity of age was tested against mortality and an a priori interaction of age and OA. The multivariable model was adjusted for the same confounders as above: age, sex, and race.

2.4.3. IPD Meta-analysis

Meta-analysis involves estimating an appropriate summary statistic for each study and then the calculation of a weighted average of these statistics across studies (25). A meeting of biostatistics and IPD meta-analysis experts was convened to determine the most appropriate statistical methodology for combining data from multiple prospective population-based cohorts, which were not originally designed for this purpose. **Appendix 7** shows the list of experts and their academic affiliations. The experts recommended using IPD meta-analysis methods starting with a two-stage approach before attempting a one-stage analysis. A two-stage IPD meta-analysis consists of two distinct parts: first, each cohort is analysed individually using identical methodology; second, the result of each individual analysis is pooled using standard meta-analysis statistical methods (26).

Data was pooled using random effects analysis, with Dersimonian and Laird estimation. Heterogeneity was assessed using I^2 and the Tau statistic. Pooled estimates were produced for subgroups and not for the overall analysis due to the high degree of heterogeneity between

subgroups. Pooled estimates were also produced where cohorts were limited to non-side specific joint pain data (Rotterdam and TasOAC).

Hazard ratios (HR) and 95% confidence intervals (CI) were produced for each cohort and then were used with the Stata metan command to produce forest plots and pooled estimates (27).

All analyses were conducted using Stata version 13.0 statistical software (StataCorp, College Station, Texas, USA).

3. RESULTS

3.1. Prevalence of Osteoarthritis and Mortality

3.1.1. Osteoarthritis

Eight cohorts contributed data to the symptomatic radiographic knee OA analysis (six in the SROA, seven in the SOA time-to-event analysis). The number of baseline subjects ranged from 683 to 3762 in each cohort, totaling 14,654 subjects for the knee analyses (**table 3**). Subjects from US-based cohort studies totaled 7,577. Prevalence of SROA in subjects ranged from 4.4% in one of the youngest cohorts (Chingford) to 33.3% in a cohort enriched with subjects at higher risk of OA (MOST). Four cohorts, with 16,134 subjects, contributed data to the hip pain analysis. Between 15.8% and 41.0% of subjects had hip pain (with or without ROA) at baseline in the four cohorts with hip data (**table 4**).

Table 3. Prevalence of symptomatic radiographic Knee OA

Cohort	Baseline Age Mean (SD)	N	Baseline Osteoarthritis (%)			
			None	Pain-/ROA +	Pain+/ROA-	Pain+/ROA+
Chingford	57.9 (6.0)	683	483 (70.7%)	129 (18.9%)	41 (6.0%)	30 (4.4%)
Hertfordshire	64.8 (2.6)	817	445 (54.5%)	45 (5.5%)	242 (29.6%)	85 (10.4%)
Johnston County	59.8 (9.4)	3762	1,707 (45.4%)	378 (10.1%)	1,023 (27.2%)	654 (17.4%)
MOST	62.5 (8.1)	2906	827 (28.5%)	503 (17.3%)	608 (20.9%)	968 (33.3%)
Rotterdam	69.8 (5.1)	2813	1,750 (62.2%)	293 (10.4%)	454 (16.1%)	316 (11.2%)
Framingham	60.0 (7.6)	886	594 (67.0%)	63 (7.1%)	181 (20.4%)	48 (5.4%)
TasOAC	64.4 (7.9)	410	96 (23.4%)	157 (38.3%)	42 (10.2%)	115 (28.1%)
ROAD	68.9 (8.6)	2354	980 (41.6%)	848 (36.0%)	122 (5.2%)	404 (17.2%)

Table 4. Prevalence of symptomatic hip OA

Cohort	Baseline Age Mean (SD)	N	Hip pain	No Hip pain
SOF	70.4 (3.8)	8055	2382 (29.6%)	5673 (70.4%)
Johnston County	60.0 (9.5)	3845	1,413 (36.8%)	2,432 (63.3%)
TaSOAC	64.4 (8.0)	439	180 (41.0%)	259 (59.0%)
Rotterdam	69.9 (5.1)	3795	601 (15.8%)	3,194 (84.2%)

3.1.2. Mortality

Median follow up for this analysis ranged from 5.6 (5.5, 5.8) to 19.8 (19.1, 20.4) years after baseline. There was substantial variability in the age at baseline and the duration of follow up in each cohort, such that the percentage of subjects that died in each cohort ranged from 2.9 to 57.9% (**table 5**).

Table 5. Mortality data in cohorts

Cohort	Joint	N	Max Follow-up (yrs)	Median Follow-up (yrs)	Follow-up, Range	Mortality
Chingford	Knee	683	22.5 years	19.8 (19.1, 20.4)	0.13 - 22.5	127 (18.6%)
Hertfordshire	Knee	817	11.4 years	9.6 (8.7, 10.5)	2.32-11.4	67 (8.2%)
Johnston County	Knee	3762	23.7 years	11.6 (9.0, 17.7)	0.07-23.7	1,348 (35.8%)
Johnston County	Hip (pain only)	3845	23.7 years	11.6 (8.9, 17.7)	0.04-23.6	1,393 (36.2%)
MOST	Knee	2906	7.4 years	5.6 (5.5, 5.8)	0.16 - 7.4	84 (2.9%)
SOF	Hip (pain only)	8055	23.3 years	16.6 (11.4, 20.5)	0.02 - 23.3	4660 (57.9%)
Rotterdam	Knee	2813	17.8 years	14.3 (9.8, 15.6)	0.2-17.8	1412 (50.2%)
Rotterdam	Hip (pain only)	3795	17.8 years	14.1 (9.2, 15.6)	0.2-17.8	1,972 (52.0%)
TaSOAC	Knee	410	13.6 years	6.4 (2.9, 10.6)	0.04-13.6	128 (31.2%)
TasOAC	Hip (pain only)	439	13.4 years	6.4 (2.9, 10.5)	0.04-13.6	136 (31.0%)
Framingham	Knee	886	13.9 years	11.9 (10.9, 12.6)	1.7-13.9	68 (7.7%)
ROAD	Knee	2354	7 years			90 (3.8%)

3.2. Kaplan-Meier Plots

Example survival estimate curves and 95% CIs are shown for knee SROA and hip symptomatic OA from the Framingham and Johnston County cohort studies (**figures 1- 3**).

Figure 1. Kaplan-Meier plot for knee SROA in Johnston County cohort (truncated at 20 years follow up)

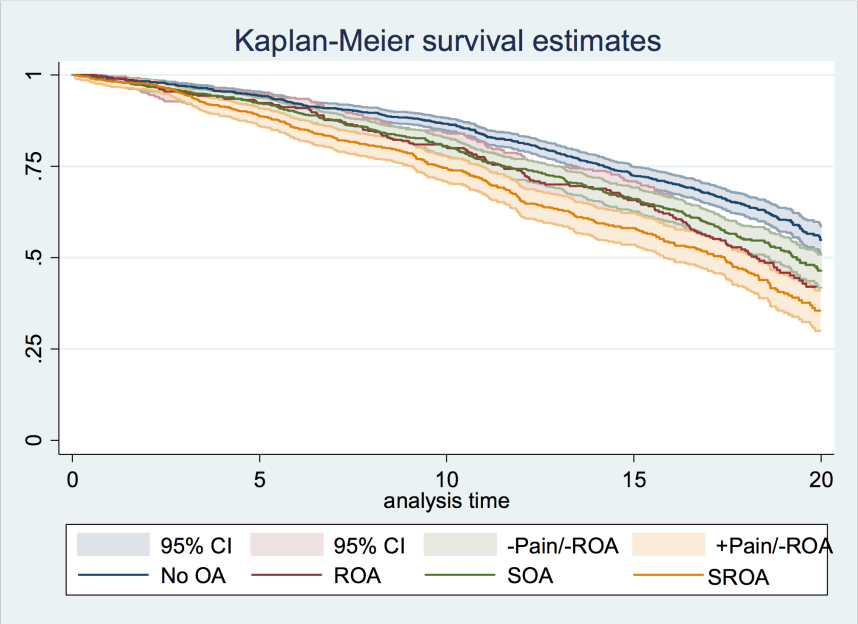


Figure 2. Kaplan-Meier plot for knee SROA in Framingham cohort (truncated at 12 years follow up)

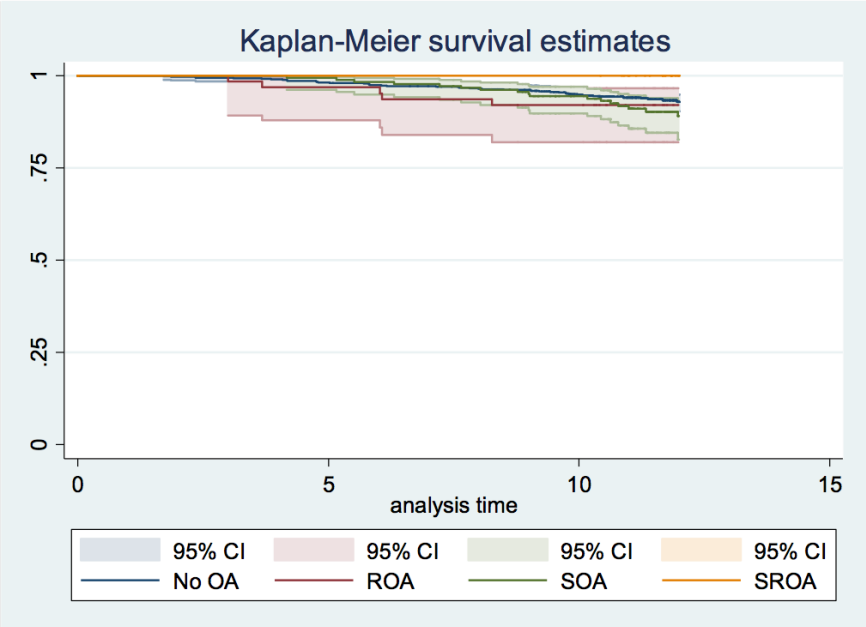
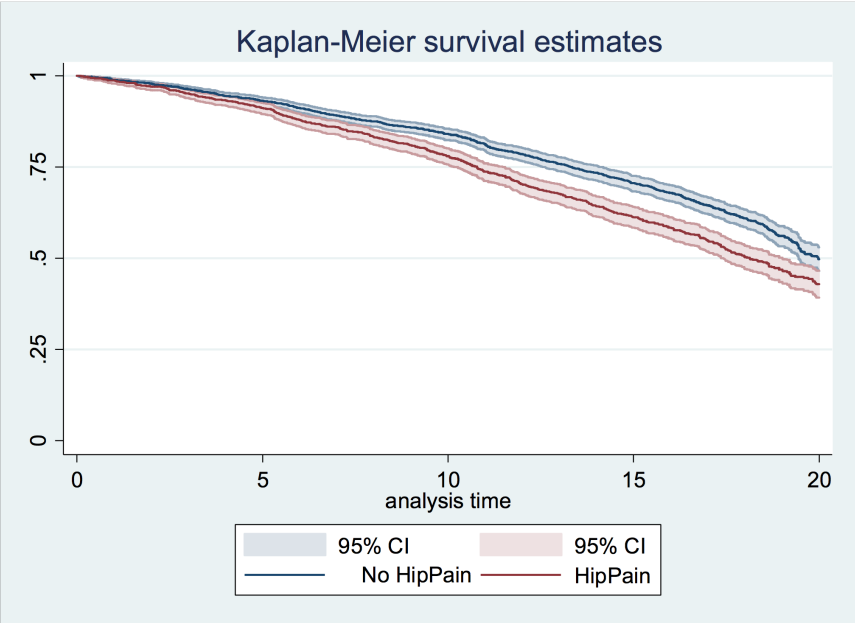


Figure 3. Kaplan-Meier plot for hip pain in the Johnston County cohort (truncated at 20 years follow up)

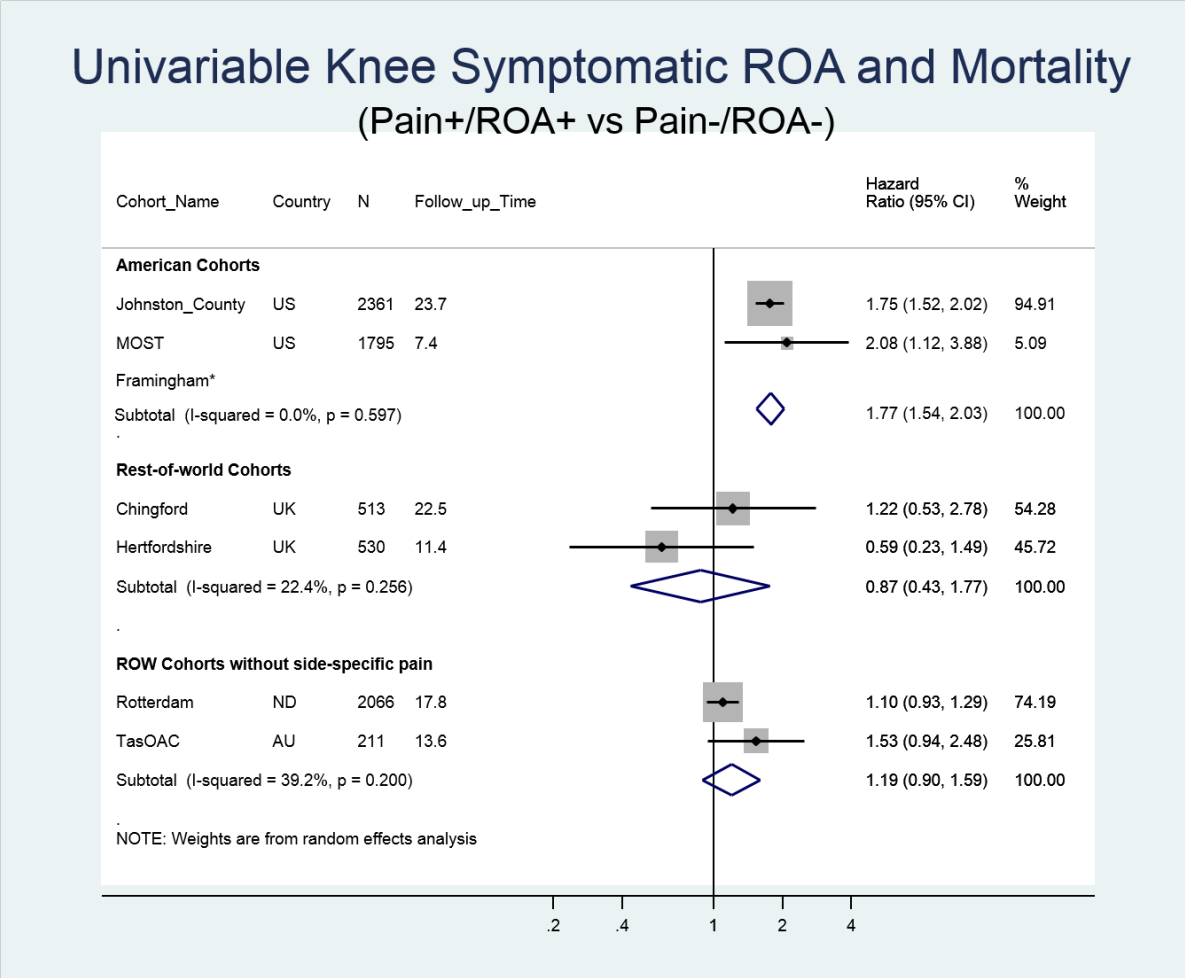


3.3. Meta-analysis of Symptomatic Radiographic Knee Osteoarthritis (Pain+/ROA+ vs Pain-/ROA-)

This analysis compared subjects who had both pain and radiographic OA in the same joint (Pain+/ROA+) at baseline against subjects who had no OA. It is important to note that this control group contained participants who could have reported pain for up to 14 days per month and therefore could have suffered from early/mild OA. The Framingham cohort was not included in this analysis due to the very low number of subjects having the outcome of interest.

In the unadjusted analysis, subjects with symptomatic radiographic knee OA (SROA) in the MOST cohort had the highest risk of premature death (HR 2.08 [95% CI 1.12, 3.88]), with Johnston County the next highest (HR 1.75 [95% CI 1.52, 2.02]). The pooled estimate for the American subgroup of cohorts was HR 1.77 (95%CI 1.54, 2.03). The UK, European and Australian cohorts had no significant association between OA and mortality (**figure 4**).

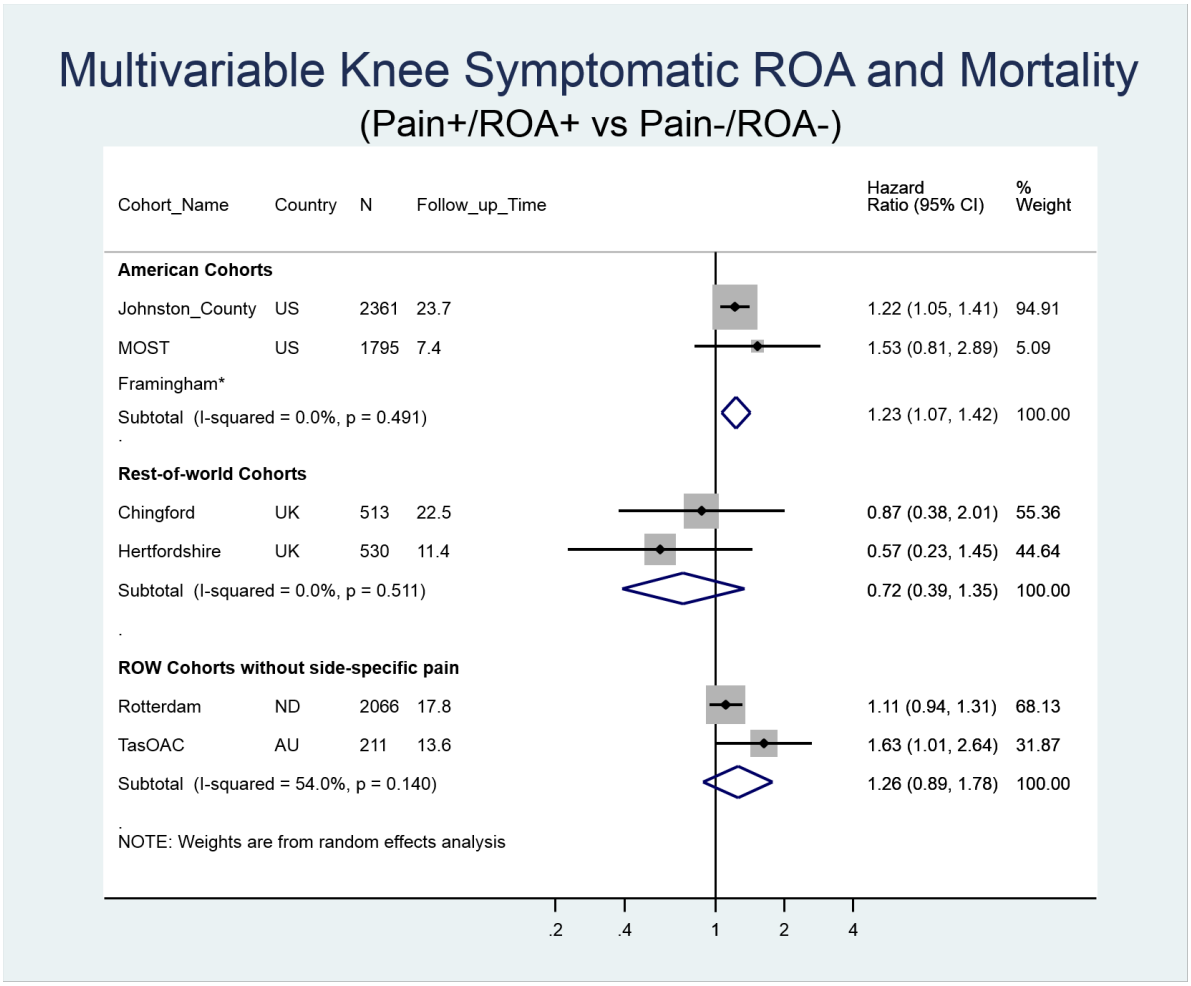
Figure 4. Univariable SROA Forest Plot



*The Framingham cohort was omitted from this analysis due to the very low number of subjects having the outcome of interest.

The results of the multivariable analysis were attenuated slightly in all cohorts. The pooled estimate for the US subgroup showed a 23% increased risk of premature mortality with SROA (95%CI 1.07, 1.42). TasOAC showed an increased risk by 63% (95% CI 1.01, 2.64), however no other ROW cohorts showed a significant associations. The pooled estimates remained non-significant for both the ROW cohorts (HR 0.72, 95% CI 0.39, 1.35) and the ROW cohorts without side-specific pain (HR 1.26 (95%CI 0.89, 1.78)) (**figure 5**). Unadjusted and fully adjusted logistic regression analysis of the ROAD cohort also showed no association with mortality (OR 0.60 95% CI 0.30, 1.20 and OR 0.69 95% CI 0.33, 1.42, respectively).

Figure 5. Multivariable SROA Forest Plot (adjusted for age, sex, and race)



*The Framingham cohort was omitted from this analysis due to the very low number of subjects having the outcome of interest.

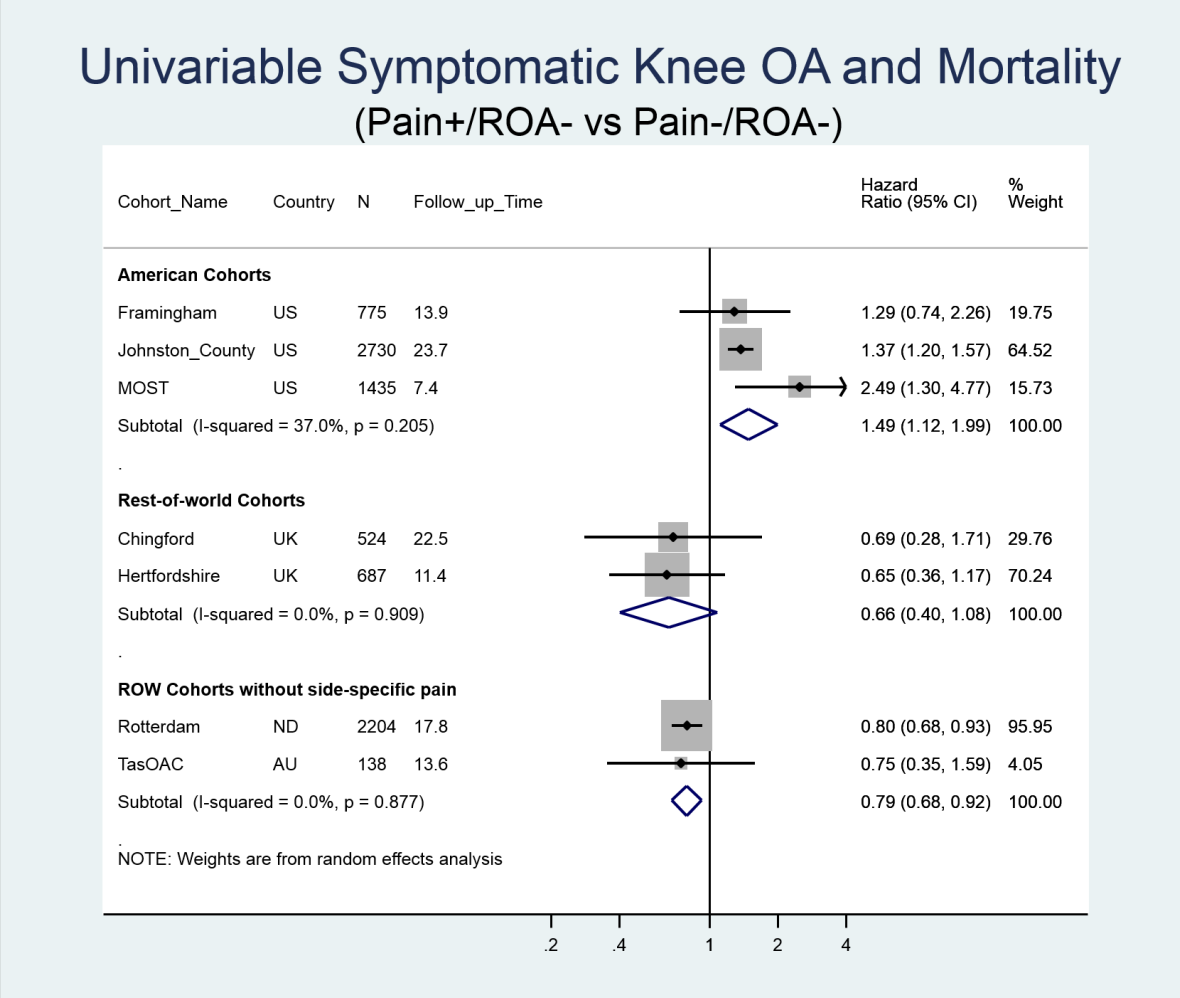
3.4. Meta-analysis of Symptomatic Knee Osteoarthritis (without ROA) (Pain+/ROA- vs Pain-/ROA-)

This analysis compared subjects who have pain and no radiographic OA (Pain+/ROA-) against subjects without pain and ROA. It is important to note that this control group contained participants who could have reported pain on up to 14 days per month and therefore could have suffered from early/mild OA.

In the univariable analysis of subjects with symptomatic knee OA (no ROA), the data from the US subgroup showed a 49% increased risk of premature mortality (95% CI 1.12, 1.99), with the ROW subgroup showing a non-significant association (HR 0.66, 95% CI 0.40, 1.08)

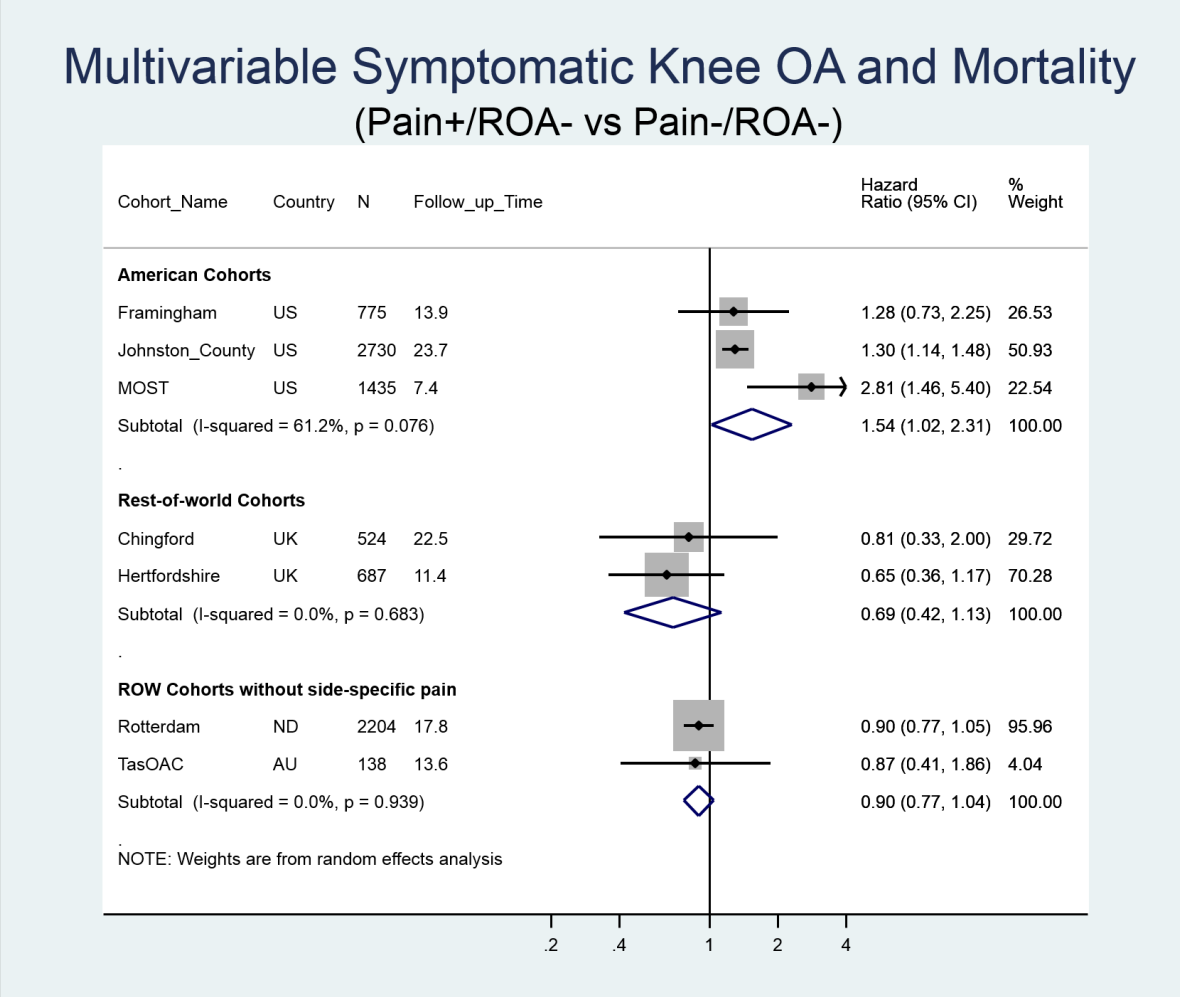
and the non side-specific pain ROW group showing a significantly protective hazard ratio of 0.79 (95% CI 0.68, 0.92). (**figure 6**).

Figure 6. Univariable SOA Forest Plot



When adjusted for age, sex and race, the US subgroup had a 54% increased risk of premature mortality (95% CI 1.02, 2.31), while the ROW group remained non-significant (HR 0.69, 95% CI 0.42, 1.13) (**figure 7**). The ROW non side-specific pain group became non-significant in the fully adjusted model (HR 0.90, 95% CI 0.77, 1.04). Unadjusted and fully adjusted logistic regression analysis of the ROAD cohort also showed no association with mortality (OR 0.39 95% CI 0.09, 1.64 and OR 0.46 95% CI 0.11, 1.96, respectively).

Figure 7. Multivariable SOA Forest Plot adjusted for age, sex and race



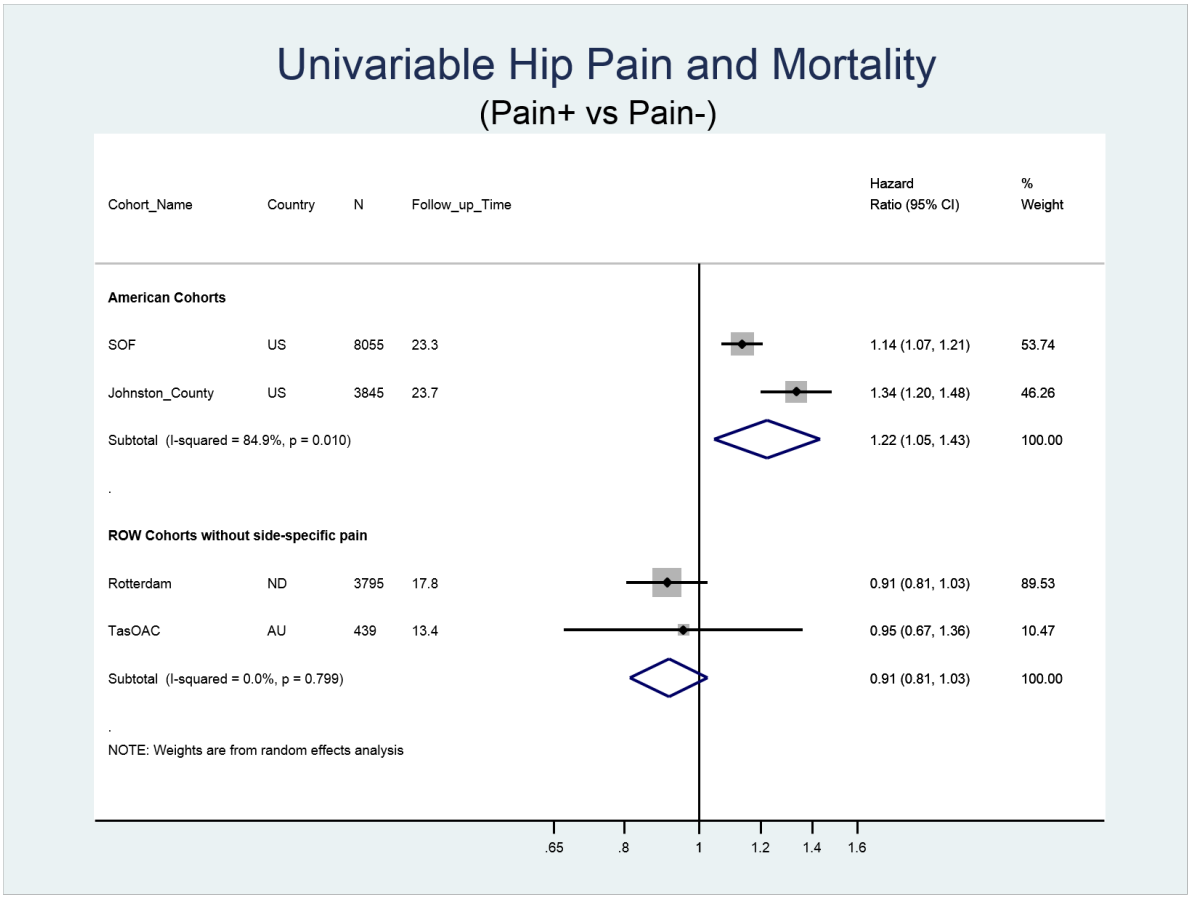
These results confirm an increased risk of premature mortality in the US cohorts with an adjusted HR of 1.23 for SROA and 1.54 for symptomatic knee OA (without ROA). The data from the European and Australia cohorts did not find any significant association with mortality except in the case of the ROW cohorts without side-specific pain. The pooled estimate showed a significantly protective effect of SOA on mortality (HR 0.79), however, this association became non-significant once adjusted for age and sex. It is interesting to note, and explore, that the cohorts with no increased risk, tended to be those with the lowest number of deaths.

3.5. Symptomatic Hip OA (pain presence regardless of ROA status)

This analysis compared subjects who had hip pain (regardless of radiographic OA) at baseline against subjects who had no hip pain.

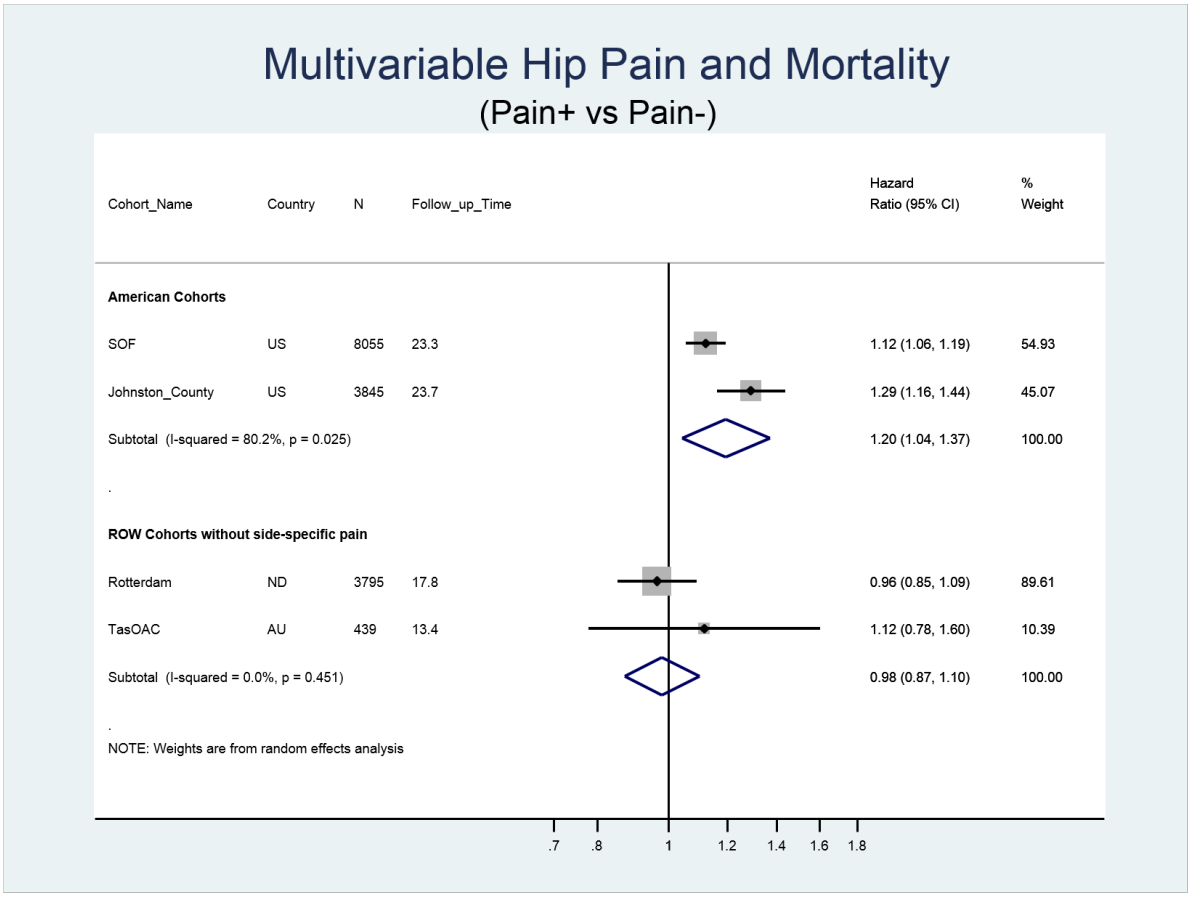
In the univariable analysis of subjects with hip pain, the data from the US subgroup showed a 22% increased risk of premature mortality (95% CI 1.05, 1.43). The ROW cohorts had a non-significant association (HR 0.91, 95% CI 0.81, 1.03) (**figure 8**).

Figure 8. Univariable Hip Pain (regardless of ROA status) analysis



When adjusted for age, sex and race, the US subgroup had a 20% increased risk of mortality (95% CI 1.04, 1.37) and the ROW cohorts remained non-significant (HR 0.98, 95% CI 0.87, 1.10) (**figure 9**).

Figure 9. Multivariable Hip Pain (regardless of ROA status) analysis adjusted for age, sex and race



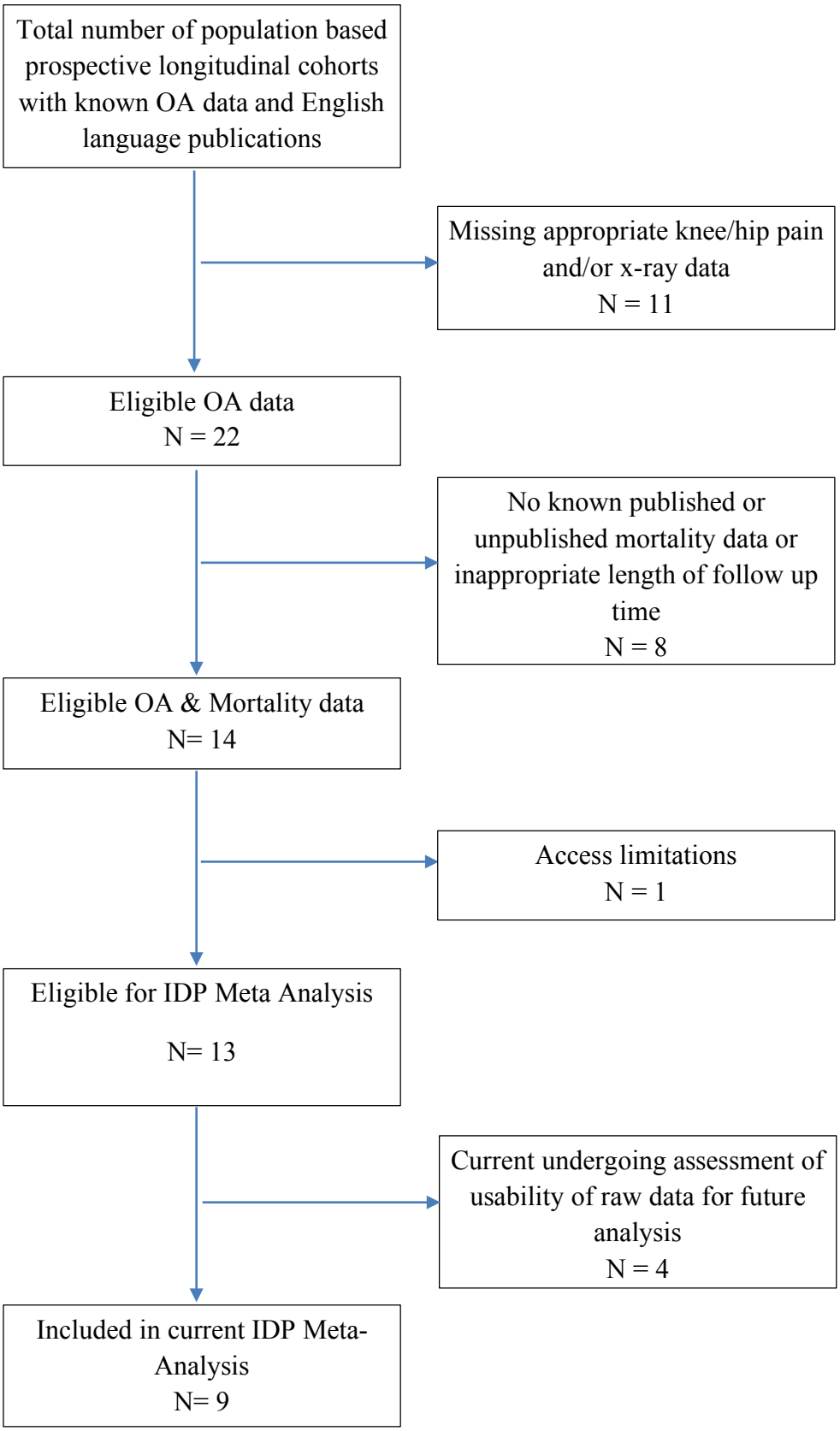
4. Key Findings

Subjects in the US cohorts with symptomatic radiographic knee osteoarthritis were 23% more likely to die prematurely than subjects free from OA, independent of age, sex and race. Subjects with symptomatic knee OA (without ROA), had an even higher risk of premature mortality with a 54% increased risk in the adjusted model. US subjects with hip pain had an increased risk of 20% compared to subjects without.

No association was found in the ROW cohorts between osteoarthritis (knee SROA, knee SOA, or hip pain) and premature mortality.

ROW cohorts without side-specific pain showed a protective association between symptomatic OA (SOA) and mortality, however, this association disappeared after the adjustment for age, sex and race.

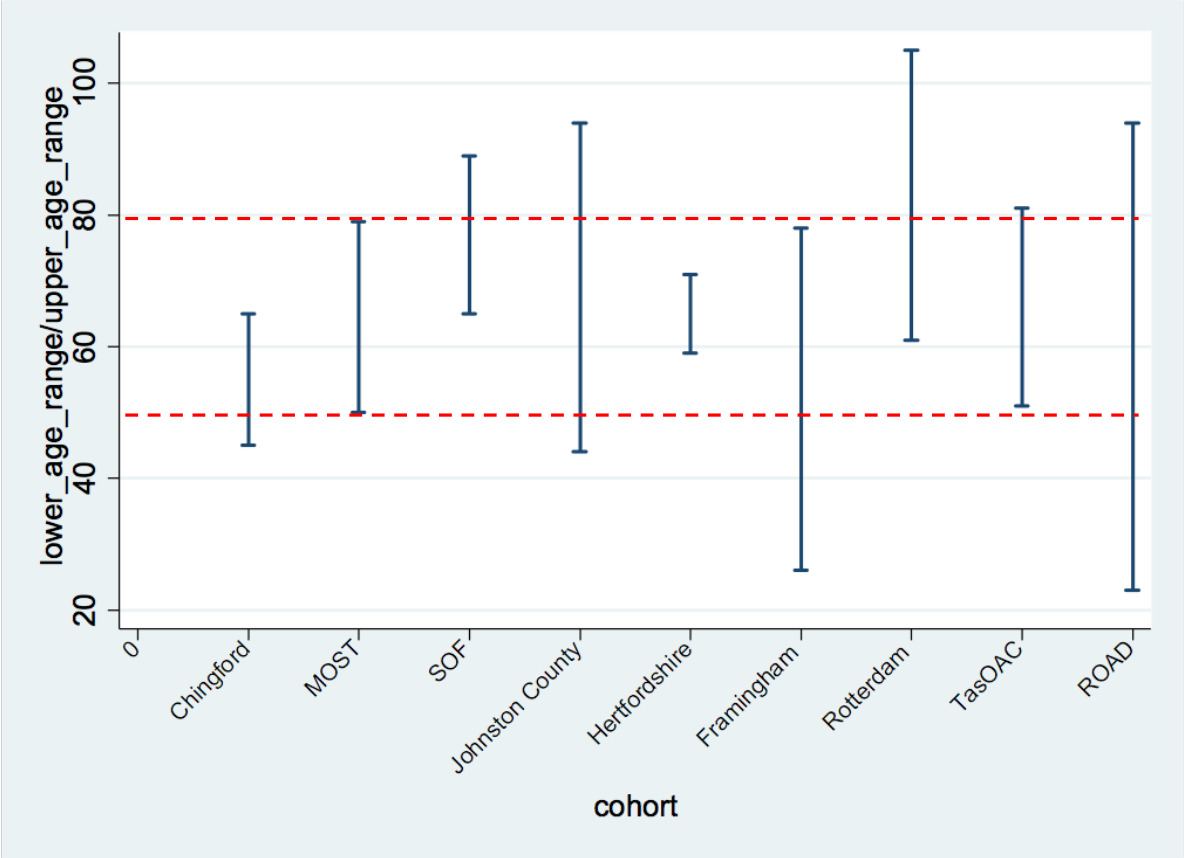
Appendix 1. Cohort selection



Appendix 2. Harmonisation of variables

a) Harmonisation of age

Figure 10. Original and newly truncated age ranges for each cohort



----- Age truncated to 45- 80 years

b) Harmonisation the main risk factor and confounders

	Radiographic Knee/Hip OA	**Knee/Hip Joint pain**	**Sex**	**Race**	**Rheumatoid Arthritis**
Final harmonised variable	Symptomatic Radiographic OA based on radiographic OA and self-reported pain		Male/ female	1. Caucasian 2. African American 3. Japanese 4. Asian 5. Indigenous Australian 6. Hispanic 7. Other	1. Rheumatoid Arthritis present 2. Rheumatoid Arthritis absent
Chingford	How many days in the last month have you had knee pain?	K&L knee grade 0-4	Female	Caucasian	Rheumatoid Arthritis: Yes/no
Hertfordshire	Knee pain in last month?	K&L knee grade 0-4	Male & female	Caucasian	No Rheumatoid Arthritis variable in dataset

Rotterdam	In the past month have you suffered pain or other complaints in the knee, back, hips or hand joints? Do you suffer from pain or stiffness in the knee (non-side specific)? (same for hip) How long have you had these complaints in the knee? (same for hip) - < 1 month - 1 to 3 months - 3 to 6 months - 6 mnths to 1 yrr - 1 to 5 years - >= 5 years	K&L knee grade 0-4 K&L hip grade 0-4	Male & female	No race variable available in required dataset	No Rheumatoid Arthritis variable available at required time point in dataset

JoCo	Knee/hip pain severity: None Mild Moderate Severe	K&L knee grade 0-4 K&L hip grade 0-4	Male & female	-Caucasian -African American	No Rheumatoid Arthritis variable in dataset
SOF	Knee pain lasting at least a month in the last year?	OARSI Atlas. Individual features (osteophytes and joint space narrowing)	Female	-Caucasian -other	Rheumatoid Arthritis: Yes/No
Framingham	On most days do you have pain, aching or stiffness in either of your knees? Is the pain aching or stiffness in your right knee, left knee, or both knees?	K&L knee grade 0-4	Male & female	-Caucasian -African American -Asian -other	Rheumatoid Arthritis: Yes/No

MOST	Knee pain lasting most days in the last month?	K&L knee grade 0-4	Male & female	-Caucasian -Black or African American -other	Rheumatoid Arthritis: Yes/No
TaSOAC	Do you have hip pain (non-side specific)? WOMAC knee pain scale (non-side specific)	Altman Atlas Grading (0-3)	Male & female	-Caucasian -African American -Japanese -Asian -Indigenous Australian -Hispanic -other	Rheumatoid Arthritis: Yes/No
ROAD	Pain in and around the knee joint on most days during the past month?	K&L knee grade 0-4	Male & female	No race variable available in dataset	No Rheumatoid Arthritis variable in dataset

Appendix 3. List of experts and institutions from osteoarthritis consensus meeting

Expert	Institution
Michael Nevitt	UCSF, United States
David Felson	Boston, United States
Kirsten Ambrose	UNC, United States
Marc Hochberg	Maryland, United States
Stefan Lohmander	Lund, Sweden
Phil Conaghan	Leeds, United Kingdom
Joyce van Meurs	Erasmus MC, Netherlands
Sita Bierma-Zeinstra	Erasmus MC, Netherlands
Ewa Roos	USD, Denmark
Kate Jackson	Oxford, United Kingdom
Cyrus Cooper	Southampton, United Kingdom
Julia Newton	Oxford, United Kingdom
Mark Batt	Nottingham, United Kingdom
Joanne Jordan	UNC, United States
Noriko Yoshimura	Tokyo, Japan
Graeme Jones	UTAS, Australia
David Hunter	Sydney, Australia
Lars Engebretsen	Oslo, Norway

Appendix 4. OARSI pain abstract

Measuring the variation between self-reported osteoarthritis pain assessments

Authors: Leyland, K.M.[1], Gates, L.S.[1,2], Nevitt, M. [3], Felson, D. [4], Ambrose, K.[5], Bierma-Zeinstra, S.M.[6], Conaghan, P.G.[7], Engebretsen, L.[8], Hochberg, M.[9], Hunter, D.[10, 11], Jones, G.[12], Jordan, J.M.[5,13], Judge, A.[1] Lohmander, S.[14], Roos, E.M.[15],Sanchez-Santos, M.T.[1] , Sheard, S.[1], Yoshimura, N.[16], van Meurs, J.B.J.[17], Batt, M.E.[18], Newton, J.[1], Cooper, C. [1,2], Arden, N. [1,2]

[1]NIHR Musculoskeletal Biomedical Research Unit and Arthritis Research UK Centre for Sport, Exercise, and Osteoarthritis, University of Oxford, Oxford, UK
[2] MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
[4]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA
[5]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC USA
[6]Department of Orthopaedics, Erasmus University Medical Centre, Rotterdam, the Netherlands
[7]University of Leeds, Leeds, UK
[8]Department of Orthopaedic Surgery, Oslo University Hospital and Oslo Sports Trauma Research Center, Norwegian School of Sports Sciences, Oslo, Norway
[9]University of Maryland School of Medicine, Baltimore, USA
[10]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia
[11]Rheumatology Department, Royal North Shore Hospital, St Leonards, Sydney, Australia
[12]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia
[13]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC USA
[14]Lund University, Lund, Sweden and University of Southern Denmark and Odense University Hospital, Odense, Denmark
[15] Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

[16]Department of Joint Disease Research, 22nd Century Medical & Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan
[17]Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[18]Centrefor Sports Medicine, Nottingham University Hospitals and Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, Nottingham, UK

Purpose

Self-reported pain questions are the established way to determine osteoarthritis (OA) related pain in population cohort studies, of which NHANES-type (National Health Nutrition Examination Survey) questions and WOMAC (Western Ontario and McMaster Universities Arthritis Index) are the most common. However, there is limited understanding of how wording variations relating to the duration of pain (i.e. most days in the month) and period of pain recall (i.e. in the last year) affect the prevalence and comparability of these questions. The aim of this research was to assess four common NHANES pain questions and to establish an equivalent threshold within the WOMAC pain subscale.

Methods

An expert consensus meeting was convened to determine the best method to harmonise OA data among international cohorts. The Multicenter Osteoarthritis Study (MOST) was suggested as the best cohort to examine the relationship of OA-pain assessments as it contains multiple NHANES questions in addition to WOMAC, which is representative of the questions used in international cohorts. The MOST study is a US-based observational study of subjects with or at high risk for knee OA recruited in 2003. Participants at baseline completed the WOMAC pain subscale (range 0-20) asking for pain during daily activities in the past 30 days and answered four binary NHANES-type questions: A) Knee pain lasting most days in the last month; B) Any knee pain in the last month; C) Knee pain lasting at least a month in the last year; D) Any knee pain in the last year.

Sensitivity, specificity and area under the curve (AUC) from ROC curves were used to compare NHANES-type questions, with NHANES A as the gold-standard. A cut-point was established for the WOMAC pain subscale against the gold standard at the point at which sensitivity and specificity were closest together. 95% confidence intervals (CI) around the

cut-points were estimated using bootstrap methods with 300 repeats. The Osteoarthritis Initiative cohort (OAI), which has similar inclusion criteria to MOST, was used to validate the WOMAC threshold against the NHANES A question using the same methods.

Results

2922 subjects out of 3026 had all required data at baseline (basic demographics and pain questions) and were used for the cross-sectional analysis. NHANES A and C showed a similar prevalence of pain (41.0% and 43.4%), while NHANES B and D showed similar but higher prevalence (67.3% and 75.4%). NHANES C (pain lasting at least a month in the last year) showed the best sensitivity (91.2%) and specificity (89.9%) against the gold-standard NHANES A, with both NHANES B and D having very low specificity (55.5% and 41.7% respectively) (**table 1**).

The WOMAC pain subscale had a median of 2 (IQR 0, 6), and a cut point of 3 was found using both NHANES A (3 (95% CI 2.1, 3.9)) and C (3 (95%CI 2.8, 3.2)). When this cut-point was used to create a binary pain variable from the WOMAC pain subscale, the sensitivity and specificity of this new variable against the NHANES A question was 83.6% and 76.0%, respectively. In the OAI validation cohort (n=4,723), the WOMAC pain subscale had a median of 1 (IQR 0, 4) and also generated a cut-point of 3 (95% CI 2.3, 3.7).

Conclusion

Prevalence of pain varied between 41.0 and 75.4% depending on the wording of the NHANES-type question. Comparability of questions was influenced more by the duration of reported pain (i.e. pain lasting at least a month) than the period of pain recall (i.e. in the last year). NHANES C had the best sensitivity and specificity against the gold-standard NHANES A. A cut-point of 3 in the WOMAC pain subscale was identified as having the best sensitivity and specificity against both NHANES A and NHANES C. The same cut-point of 3 was found in the validation cohort. This research highlights the effect that wording variations may have on the prevalence of OA-related pain and provides the most comparable pain questions/thresholds against the current gold-standard.

Table 1. Comparison of NHANES-type pain questions and WOMAC binary cut-off 3+ in MOST*

	Prevalence (N)	Sensitivity	Specificity	AUC (95% CI)
NHANES A	41.0% (1198)	*gold standard*	*gold standard*	*gold standard*
NHANES B	67.3% (1966)	100.0%	55.5%	0.78 (0.77, 0.79)
NHANES C	43.4% (1267)	91.2%	89.9%	0.91 (0.90, 0.92)
NHANES D	75.4% (2203)	100.0%	41.7%	0.71 (0.70, 0.72)
WOMAC cutoff 3+	48.4% (1415)	83.6%	76.0%	0.80 (0.78, 0.81)

*Out of whole sample (n=2922)

Appendix 5. Cohort baseline demographics for complete case vs subjects with any missing values (risk factor or confounders) for knee OA

Table 1. Johnston County complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case		Missing Values		p-value
N = 3918	3,762		156		
SROA					
None	1,707	(45.4%)	0		
ROA Only	378	(10.1%)	0		
Pain Only	1,023	(27.2%)	0		
ROA and Pain	654	(17.4%)	0		
Age	59.8	(9.4)	63.3	(10.4)	0.000
Sex (% female)	2,348	(62.4%)	109	(69.9%)	0.059
Race					
Caucasian	2,466	(65.6%)	102	(65.4%)	0.966
African American	1,296	(34.5%)	54	(34.6%)	
BMI (continuous)	29.7	(6.4)	29.3	(6.1)	0.4253
Ex/current Smoking (binary)	1885	(51.1%)	48	(44.0%)	0.145
CVD2 (heart/stroke)	1057	(28.1%)	41	(26.3%)	0.621
Diabetes	487	(13.0%)	22	(14.5%)	0.588

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 2. Hertfordshire complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	**Complete Case**	**Missing Values**	**p-value**
N = 957	817	140	
SROA			
None	445 (54.5%)	0	
ROA Only	45 (5.5%)	0	
Pain Only	242 (29.6%)	0	
ROA and Pain	85 (10.4%)	0	
Age	64.8 (2.6)	64.7 (2.5)	0.4338
Sex (% female)	405 (49.6%)	54 (38.6%)	0.016
Race	NA	NA	
BMI (continuous)	27.0 (4.3)	27.5 (4.4)	0.1629
Ex/current Smoking (binary)	412 (50.5%)	91 (65.0%)	0.001
CVD2 (heart/stroke)	93 (11.4%)	22 (15.7%)	0.145
Diabetes	96 (11.8%)	17 (12.2%)	0.903

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 3. ROAD complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case	Missing Values	p-value
N = 2376	2,354	22	
SROA			
None	980 (41.6%)	0	
ROA Only	848 (36.0%)	0	
Pain Only	122 (5.2%)	0	
ROA and Pain	404 (17.2%)	0	
Age	68.9 (8.6)	75.2 (2.2)	0.0002
Sex (% female)	1,531 (65.0%)	13 (59.1%)	0.561
Race	NA	NA	
BMI (continuous)	23.2 (3.5)	23.8 (2.0)	0.2266
Ex/current Smoking (binary)	631 (29.4%)	5 (33.3%)	0.741
CVD2 (heart/stroke)	NA	NA	
Diabetes	NA	NA	

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 4. Framingham complete case vs subjects with any missing values for risk factor and confounders*-

Baseline Variable	Complete Case	Missing Values	p-value
N = 905	886	19	
SROA			
None	594 (67.0%)	0	
ROA Only	63 (7.1%)	0	
Pain Only	181 (20.4%)	0	
ROA and Pain	48 (5.4%)	0	
Age	56.0 (7.6)	57.2 (7.6)	0.466
Sex (% female)	461 (52.0%)	13 (68.4%)	0.157
Race			
Caucasian	886 (100%)	19 (100%)	
BMI (continuous)	27.3 (4.6)	26.8 (3.1)	0.809
Ex/current Smoking (binary)	568 (64.2%)	12 (63.2%)	0.927
CVD2 (heart/stroke)	30 (3.4%)	0	
Diabetes	39 (4.4%)	1 (5.3%)	0.860

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 5. Chingford complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case		Missing Values		p-value
N = 857	683		174		
SROA					
None	483	(70.7%)	0		
ROA only	129	(18.9%)	0		
pain only	41	(6.0%)	0		
ROA and pain	30	(4.4%)	0		
Age	57.9	(6.0)	58.1	(5.9)	0.697
BMI (continuous)	26.3	(4.4)	26.4	(4.3)	0.735
Ex/current Smoking (binary)	317	(46.4%)	70	(40.2)	0.143
CVD2 (heart/stroke)	25	(4.3%)	10	(7.4%)	0.134
Diabetes	6	(0.9%)	3	(1.7%)	0.329

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 6. MOST complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case	Missing Values	p-value
N = 2936	2906	30	
SROA			
None	827 (28.5%)	0	
ROA Only	503 (17.3%)	0	
Pain Only	608 (20.9%)	0	
ROA and Pain	968 (33.3%)	0	
Age	62.5 (8.1)	64.3 (6.9)	0.215
Sex (% female)	1759 (60.5%)	16 (53.3%)	0.423
Race			
Caucasian	2449 (84.3%)	21 (70.0%)	
African American	418 (14.4%)	8 (26.7%)	0.058
Other	39 (1.3%)	1 (3.3%)	
BMI (continuous)	30.7 (5.9)	30.4 (6.7)	0.805
Ex/current Smoking (binary)	1292 (44.5%)	13 (43.3%)	0.902
CVD2 (heart/stroke)	335 (11.9%)	4 (13.8%)	0.749
Diabetes	304 (10.7%)	3 (10.0%)	0.901

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 7. Rotterdam complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case	Missing Values	p-value
N = 3848	2813	1035	
SROA (no-side specific pain)			
None	1,750 (62.2%)	0	
ROA Only	293 (10.4%)	0	
Pain Only	454 (16.1%)	0	
ROA and Pain	316 (11.2%)	0	
Age	69.8 (5.1)	70.2 (5.3)	0.0170
Sex (% female)	1,554 (55.2%)	652 (63.0%)	0.000
Race	NA	NA	
BMI (continuous)	26.9 (3.9)	27.0 (4.2)	0.6050
Ex/current Smoking (binary)	1,979 (70.4%)	680 (68.8%)	0.347
CVD2 (heart/stroke)	133 (5.3%)	64 (7.1%)	0.103
Diabetes	394 (14.0%)	154 (15.1%)	0.394

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 8. TasOAC complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case	Missing Values	p-value
N = 445	410	35	
SROA (no-side specific pain)			
None	96 (23.4%)	0	
ROA Only	157 (38.3%)	0	
Pain Only	42 (10.2%)	0	
ROA and Pain	115 (28.1%)	0	
Age	64.4 (7.9)	65.1 (8.7)	0.6464
Sex (% female)	209 (51.0%)	18 (51.4%)	0.959
Race			
Caucasian white	263 (98.1%)	19 (100%)	0.835
Asian	2 (0.8%)		
Indigenous Australian	3 (1.1%)		
BMI (continuous)	28.2 (5.2)	27.6 (4.0)	0.4707
Ex/current Smoking (binary)	224 (54.6%)	20 (58.8%)	0.637
CVD2 (heart/stroke)	44 (11.7%)	5 (17.2%)	0.378
Diabetes	36 (9.6%)	4 (13.8%)	0.463

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Appendix 6. Cohort baseline demographics for complete case vs subjects with any missing values (risk factor or confounders) for hip Pain Only

Table 1. Johnston County complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case		Missing Values		p-value
N = 3918	3,845		73		
Hip pain	1413	(36.8%)	0		
Age	60.0	(9.5)	58.5	(9.7)	0.162
Sex (% female)	2413	(62.8%)	44	(60.3%)	0.664
Race					
Caucasian	2,522	(65.6%)	46	(63.0%)	
African American	1,323	(34.4%)	27	(37.0%)	0.646
BMI (continuous)	29.7	(6.4)	28.8	(6.2)	0.248
Ex/current Smoking (binary)	1921	(60.0%)	12	(42.9%)	0.392
CVD2 (heart/stroke)	1082	(28.1%)	16	(21.9%)	0.241
Diabetes	499	(13.0%)	10	(14.5%)	0.715

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 2. SOF complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	**Complete Case**	**Missing Values**	**p-value**
N = 8120	8055	65	
Hip pain	2382 (29.6%)	0	
Age	70.4 (3.8)	71.0 (4.2)	0.216
Race			
Caucasian	8027 (99.7%)	65 (100.0%)	0.999
Other	28 (0.4%)	0	
BMI (continuous)	26.5 (4.5)	27.5 (5.0)	0.087
Ex/current Smoking (binary)	3340 (41.6%)	27 (42.2)	0.924
CVD2 (heart/stroke)	1245 (19.0%)	11 (19.6%)	0.909
Diabetes	562 (7.0%)	5 (7.8%)	0.799

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 3. Rotterdam complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	**Complete Case**	**Missing Values**	**p-value**
N = 3848	3795	53	
Hip pain	601 (15.8%)	0	
Age	69.9 (5.1)	70.5 (5.4)	0.4128
Sex (% female)	2,165 (57.05	41 (77.4%)	0.003
Race	NA	NA	
BMI (continuous)	26.9 (4.0)	25.1 (2.9)	0.0108
Ex/current Smoking (binary)	2655 (70.0%)	4 (57.1%)	0.460
CVD2 (heart/stroke)	197 (5.8%)	0	
Diabetes	541 (14.3%)	7 (18.4%)	0.465

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Table 4. TaSOAC complete case vs subjects with any missing values for risk factor and confounders*

Baseline Variable	Complete Case		Missing Values		p-value
N = 445	439		6		
Hip pain	180	41.00	0		
Age	64.4	(8.0%)	66.0	(6.1)	0.6454
Sex (% female)	224	(51.0%)	3	(50.0%)	0.960
Race					
Caucasian white	278	(98.2%)	4	(100%)	0.965
Asian	2	(0.7%)			
Indigenous Australian	3	(1.1%)			
BMI (continuous)	28.2	(5.1)	27.3	(2.7)	0.6753
Ex/current Smoking (binary)	241	(54.9%)	3	(60.0%)	0.820
CVD2 (heart/stroke)	49	(12.3%)	0		
Diabetes	40	(10.0%)	0		

*t-tests (or Wilcoxon-Mann-Whitney test) for continuous variables and Chi^2 tests (or Fishers exact) for categorical variables

Appendix 7. List of experts and institutions from methodology consensus meeting

Expert	Institution
Doug Altman	Oxford, United Kingdom
Gary Collins	Oxford, United Kingdom
Andrew Judge	Oxford, United Kingdom
Karel Moons	Utrecht University, Netherlands
Thomas Debray	Utrecht University, Netherlands

References

1. Hochberg MC. Mortality in osteoarthritis. Clin Exp Rheumatol. 2008;26(5):120-4.

2. Nüesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Jüni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ. 2011 2011-03-08 12:18:04;342.

3. Hawker GA, Croxford, R., Bierman, A. S., Harvey, P. J., Ravi, B., Stanaitis, I., & Lipscombe, L. L. All-Cause Mortality and Serious Cardiovascular Events in People with Hip and Knee Osteoarthritis: A Population Based Cohort Study. PLoS ONE. 2014;9(3).

4. Barbour KE, Lui L-Y, Nevitt MC, Murphy LB, Helmick CG, Theis KA, et al. Hip Osteoarthritis and the Risk of All-Cause and Disease-Specific Mortality in Older Women: A Population-Based Cohort Study. Arthritis & Rheumatology. 2015;67(7):1798-805.

5. Liu R, Kwok WY, Vliet Vlieland TPM, Kroon HM, Meulenbelt I, Houwing-Duistermaat JJ, et al. Mortality in osteoarthritis patients. Scandinavian Journal of Rheumatology. 2015;44(1):70-3.

6. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study — A large observational study of the determinants of fracture in older men. Contemporary Clinical Trials. 2005;26(5):569-85.

7. Kang X, Fransen M, Zhang Y, Li H, Ke Y, Lu M, et al. The high prevalence of knee osteoarthritis in a rural Chinese population: The Wuchuan osteoarthritis study. Arthritis Care & Research. 2009;61(5):641-7.

8. Zhang Y, Xu L, Nevitt MC, Aliabadi P, Yu W, Qin M, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing osteoarthritis study. Arthritis & Rheumatism. 2001;44(9):2065-71.

9. Verbrugge LM, Gruber-Baldini AL, Fozard JL. Age Differences and Age Changes in Activities: Baltimore Longitudinal Study of Aging. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 1996 January 1, 1996;51B(1):S30-S41.

10. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The framingham offspring study. Design and preliminary data. Preventive Medicine. 1975;4(4):518-25.

11. Jordan J, M., Linder G, F., Renner J, B., Fryer J, G. The Impact of Arthritis in Rural Populations. Arthritis Care and Research. 1995;8(4):242-50.

12. Cummings SR, Black DM, Nevitt MC, et al. Appendicular bone density and age predict hip fracture in women. JAMA. 1990;263(5):665-8.

13. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheumatic Disease Clinics of North America. 2004;30(4):783-97.

14. Hart DJ, Mootoosamy I, Doyle DV, Spector TD. The relationship between osteoarthritis and osteoporosis in the general population: the Chingford Study. Annals of the Rheumatic Diseases. 1994 March 1, 1994;53(3):158-62.

15. Syddall H, Aihie Sayer A, Dennison E, Martin H, Barker D, Cooper C, et al. Cohort Profile: The Hertfordshire Cohort Study. International Journal of Epidemiology. 2005 December 1, 2005;34(6):1234-42.

16. Hofman A, Murad SD, Duijn CM, Franco OH, Goedegebure A, Arfan Ikram M, et al. The Rotterdam Study: 2014 objectives and design update. European Journal of Epidemiology. [journal article]. 2013;28(11):889-926.

17. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort Profile: Research on Osteoarthritis/Osteoporosis Against Disability study. International Journal of Epidemiology. 2010 August 1, 2010;39(4):988-95.

18. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, et al. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis. 2008;67(9):1256-61

19. Kellegren J, Lawrence J. Radiological assessment of osteoarthritis. Ann Rheum Dis. 1957;16:494-501.

20. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis and Cartilage. 2007;15, Supplement 1:A1-A56.

21. Anderson JJ, Felson DT. Factors associatd with osteoarthritis of the knee in the first national health and nutrition examination survey (HANES I): Evidence for an association with overweight, race, and physical demands of work American Journal of Epidemiology. 1988 July 1, 1988;128(1):179-89.

22. Bellamy N, Campbell J, Stevens J, Pilch L, Stewart C, Mahmood Z. Validation study of a computerized version of the Western Ontario and McMaster Universities VA3.0 Osteoarthritis Index. Journal of Rheumatology. 1997;24(12):2413-5.

23. O'Reilly SC, Muir KR, Doherty M. Screening for pain in knee osteoarthritis: which question? Annals of the Rheumatic Diseases. 1996;55(12):931-3.

24. Kluzek S, Sanchez-Santos MT, Leyland KM, Judge A, Spector TD, Hart D, et al. Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women. Annals of the Rheumatic Diseases. 2015 November 5, 2015.

25. Bradburn MJ, Deeks JJ, Altman DG. Metan – an alternative meta-analysis command. Stata Technical Bulletin Reprints. 1998;44:4-15.

26. Thomas D, Radji S, Benedetti A. Systematic review of methods for individual patient data meta- analysis with binary outcomes. BMC Medical Research Methodology. [journal article]. 2014;14(1):1-9.

27. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. Metan: fixed- and random-effects meta-analysis. The Stata Journal 2008;1:3-28.