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The epidemiology and impact of pain in osteoarthritis

T. Neogi*

Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, USA

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SUMMARY

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease. The pain experience in knee OA in particular is well-recognized as typically transitioning from intermittent weight-bearing pain to a more persistent, chronic pain. Methods to validly assess pain in OA studies have been developed to address the complex nature of the pain experience. The etiology of pain in OA is recognized to be multifactorial, with both intra-articular and extra-articular risk factors. Nonetheless, greater insights are needed into pain mechanisms in OA to enable rational mechanism-based management of pain. Consequences of pain related to OA contribute to a substantial socioeconomic burden.

Introduction

The hallmark symptom of osteoarthritis (OA), the most common form of arthritis, is pain. This is the symptom that drives individuals to seek medical attention, and contributes to functional limitations and reduced quality of life[1–4]. Largely because of pain, lower extremity OA is well-recognized as the leading cause of mobility impairment in older adults in the US[5,6].

The scope of the problem

Approximately 27 million US adults and 8.5 million UK adults are estimated to have clinical OA defined on the basis of symptoms and physical findings[7,8]. Prevalence of OA increases with age; 13.9% of adults age 25 and older have clinical OA of at least one joint, while 33.6% of adults age 65 and older have OA[9].

In large epidemiologic studies, OA is often defined on the basis of standard radiographic assessments, such as the Kellgren and Lawrence grade. Symptomatic OA indicates the presence of both radiographic OA and symptoms (i.e., pain, aching, stiffness) in the same joint attributable to OA; as such, its prevalence is generally lower than that of radiographic OA (i.e., regardless of symptoms). For example, the prevalence of *radiographic* knee OA was 19% and 28% among adults age ≥45 years in the Framingham study and Johnston County Osteoarthritis Project, respectively, while the prevalence of *symptomatic* knee OA was 7% in Framingham and 17% in the Johnston County Osteoarthritis Project[10,11]. The prevalence of symptomatic knee OA in two UK studies ranged from 11 to 19%, and estimates of 5–15% were noted in surveys undertaken in other countries[12].

Symptomatic hip OA has been reported to be 9% in the Johnston County Osteoarthritis Project, with lower prevalence estimates of 0.7–4.4% in the UK[13,14]. The prevalence of symptomatic hand OA is higher, with the age-standardized prevalence of symptomatic hand OA being 14.4% and 6.9% in women and men, respectively, in younger Framingham cohorts[15], increasing to 26.2% and 13.4%, respectively, among those age ≥71 in an older Framingham cohort[16]. Another study reported an estimate of 8% among adults age 60 and older[17]. Incidence of symptomatic hand OA was reported to be 9.7% for women and 4% for men over a 9-year period[15].

The lifetime risk of developing symptomatic knee OA is estimated to be ~45% (40% in men and 47% in women) based upon Johnston County Osteoarthritis Project data, with risks increasing to 60.5% among persons who are obese, which is approximately double the risk of those who are of normal weight or are underweight[18]. With aging of the population and increasing obesity, the prevalence of OA is expected to rise. Indeed, an increase in prevalence of symptomatic knee OA over the past 20 years has been noted in the Framingham cohort, rising by 4.1% and 6% among women and men, respectively, intriguingly without a concomitant parallel rise in prevalence of radiographic OA[19]. Based upon National Health Interview Survey (NHIS) data, the estimated number of US adults with doctor-diagnosed arthritis, the majority of which is related to OA and likely symptomatic if it has had medical attention, is projected to increase to nearly 67 million by 2030[20].

* Address correspondence and reprint requests to: T. Neogi, 650 Albany Street, Suite X200, Clinical Epidemiology Research and Training Unit, Boston, MA 02118, USA. Tel: 1-617-638-5180; Fax: 1-617-638-5239.
E-mail address: tneogi@bu.edu.

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Clearly a substantial proportion of adults experience pain related to OA during their lifetime. Further, individuals with OA in one joint will often have OA in another joint(s), with resulting greater symptomatic burden of the disease.

The pain experience in OA

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[21] It is a complex subjective phenomenon, with each individual having a unique perception of it, influenced by biological, psychological and social factors[22]. Under normal circumstances, pain is a warning that something is wrong: pain from touching a hot stove, having injured a joint, or chest pain due to ischemia, for example. In these instances, pain plays a protective role, signaling to the individual to withdraw from the threat, rest to allow tissue healing, or seek help, etc. However, once its warning role is over, persistence or continued pain, i.e., chronic pain, is considered maladaptive.

Unlike many other pain conditions in which the underlying injury typically heals or resolves, OA is a disease that does not resolve. Thus, OA is typically accompanied by chronic pain. Whether, and to what degree, this ongoing chronic pain (i) plays an important nociceptive role, (ii) represents maladaptive pain, or (iii) reflects other aspects of the pain experience is not clear.

The pain experience among persons with OA has been evaluated through a number of qualitative research efforts. In the first qualitative study to focus explicitly on pain and related distress as well as changes in pain over time by Hawker *et al.*, individuals with hip and knee OA identified two distinct types of OA pain: one that was intermittent but generally severe or intense, and another that was a persistent background pain or aching[23]. Stages of OA-related pain could be discerned, with early stages characterized by activity-related pain, becoming more constant over time and punctuated by intermittent intense pain. A decrease in participation subsequently occurs in an attempt to avoid triggering such episodes. The more intense but less frequent pain that comes and goes (i.e., intermittent), particularly when unpredictable, had greater impact on quality of life than the 'background' (i.e., constant) pain. The pain had negative effects on mood, participation in social and recreational activities, and sleep. Similar findings were noted in another study of individuals who had a recent diagnosis of knee OA or were symptomatic but undiagnosed (i.e., "prediagnostic knee OA")[24]. The significance of intermittent knee symptoms was not clear for several years before participants became aware of development of chronic knee symptoms. They then altered activities to avoid more symptoms, until symptoms affected participation, at which time they sought medical care.

In addition to the concepts of "intermittent" and "constant" pain, the intensity of daily pain varies widely[25], although the underlying reasons for such variation are not well-understood. The quality of pain in OA also varies, with approximately one-third of individuals with knee OA using descriptors such as burning, tingling, numbness, and pins and needles to characterize their knee symptoms[26]. Such descriptors suggest that neuropathic pain may contribute to the OA pain experience, although specific nerve lesions have not been identified in OA.

Pain assessment in OA

Given the variation in pain intensity, frequency, pattern, and quality in OA, a single, simple question about pain is unlikely to adequately capture the full pain experience. Some of the variation in reported prevalence of symptomatic OA is related to differences in study design and populations examined, but importantly, it is also due to the way in which questions about knee pain were formulated. Differences in descriptors used to assess pain (e.g., "pain" vs "pain, aching, or stiffness") may elicit different responses. Duration over which pain is being assessed (e.g., "pain on most days of a month in the past year" vs "pain on most days of the past month") can be prone to recall bias. Ideally, uniform, standardized, and valid questionnaires should be used to evaluate pain, particularly to enable more precise pain phenotyping and facilitate cross-study comparisons, genetic association studies, and drug trial protocol development.

In OA cohort studies and trials, a number of approaches are typically used to assess pain. For evaluation of knee OA pain, the most common are a visual analog scale (VAS) or numerical rating scale (NRS) assessment of pain intensity; a single question about presence of "pain, aching of stiffness in or around the knee" over a specified period of time; and/or the pain subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[27] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[28]. The pain subscales of these latter two instruments assess pain experienced with specific activities. As a result, the pain and function subscale scores are highly correlated. Nonetheless, these validated instruments are responsive and are used in assessing efficacy of interventions. A number of additional validated generic pain instruments are available that are also appropriate for use in OA[29]. A meta-analysis concluded that different patient-reported outcome measures of pain severity have generally comparable responsiveness to treatment, with the single-item pain assessments with the VAS or NRS resulting in effect estimates comparable to the WOMAC pain subscale, although their mean standardized effect sizes were lower[30]. To enable meaningful interpretation of response to therapy rather than relying on mean group responses, the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) set of responder criteria were developed and validated for use in clinical trials[31]. To be considered a responder, at least a minimum threshold of relative and absolute improvement in pain or a lesser degree of absolute and relative improvement in at least two out of three domains (pain, function, patient global assessment) is required. Many of these same questions and instruments (e.g., WOMAC) can be used for hip OA; the Hip disability and Osteoarthritis Outcome Score (HOOS) is specific for hip OA[32]. To assess pain, stiffness and physical functioning in hand OA, the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) is commonly used[33].

Despite widespread use of these pain assessments, the complex pain experience of those living with OA is not adequately captured by existing measures. To address this issue, a multicenter international Osteoarthritis Research Society International/Outcome Measures in Rheumatology (OARSI/OMERACT) initiative led to development of a new measure informed by qualitative research findings that was subsequently validated. This new instrument, Intermittent and Constant OA Pain (ICOAP), assesses various facets regarding both intermittent and constant pain for the knee and hip separately, including frequency (for intermittent pain), intensity, effects on sleep and quality of life, degree of frustration or annoyance and upset or worried feelings associated with the pain, as well as whether the intermittent pain occurs without warning or after a trigger[34]. The ICOAP has recently been demonstrated to be responsive to change in intervention studies[35].

In keeping with the acknowledgment of the multidimensional nature of pain, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended six core domains and associated measures that should be considered when studying any type of chronic pain in clinical trials: pain (intensity and use of rescue medications), physical functioning (with a focus on pain interference), emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and

adverse events, and participant disposition[36,37]. Other domains related to pain in OA include fatigue, sleep, and cognition. With the increasing importance of patient-reported outcomes, the NIH-funded Patient Reported Outcomes Measurement Information System (PROMIS) provides an opportunity to collect a variety of validated patient-reported health outcomes related to physical, mental, and social well-being, in addition to pain.

Risk factors for pain in OA

In view of the complex, multidimensional nature of the pain experience in OA, it is perhaps not surprising that the underlying etiology of pain is multifactorial, most often considered in a bio-psychosocial framework (Fig. 1). A few such risk factors are discussed below.

The extent to which structural pathology in OA contributes to the pain experience has been controversial. A structure-symptom discordance in OA has been widely noted, based upon observations of weak correlations between radiographic severity of OA and pain presence or severity, although the discordance is less with more severe stages of radiographic disease[10,38–43]. In a systematic review, 15–76% of those with knee pain had radiographic OA, and 15–81% of those with radiographic OA had knee pain[44]. The extent of additional X-ray views obtained, the definition of pain symptoms, and the nature of the study sample (e.g., age, race) affected the prevalence of these findings, and therefore interpretation of the degree of concordance. For example, in studies evaluating both the tibiofemoral and patellofemoral joints that also obtained WOMAC pain assessments, a more consistent association was noted between pain severity and radiographic OA[45,46]. Supporting such findings, a randomized trial demonstrated intra-articular lidocaine to effectively decrease knee pain in comparison with placebo[47], lending further support to the notion that structural pathology within the knee must be contributing to pain.

Beyond measurement issues, there are additional reasons that contribute to an apparent discordance. As discussed above, pain is a subjective experience, influenced by a number of factors, including genetic predisposition[48,49], prior experience[50,51], expectations about analgesic treatment[52,53], current mood[54], coping strategies and catastrophizing[55], and sociocultural environment[56–58], as some examples. Without taking into account such factors that can contribute to between-person differences, assessment of the relation of structure to symptoms will be confounded. Unfortunately most such factors that contribute to individual variation in pain cannot be feasibly measured or collected in most studies. By adequately controlling for between-person differences using a within-person knee-matched approach, a strong dose–response relationship can be demonstrated between radiographic severity and pain presence, severity, and incidence (i.e., new onset)[59,60].

While such studies provide confirmation that structural pathology of OA does indeed contribute to the pain experience, radiographs do not provide insight into what particular structural pathologies may contribute to such pain. A review elsewhere in this issue examines the structural correlates of pain in greater detail (REF). In brief, based upon MRI studies, bone marrow lesions, synovitis, and effusions appear to have the greatest evidence supporting their relation to pain in OA to date[61].

Although such studies have highlighted the importance of structural pathology to pain in OA, attempts at structure modification have been largely unsuccessful to date with regards to pain. Some recent exceptions include promising pain results from trials evaluating zoledronic acid targeting bone marrow lesions, with possible additional bone and cartilage effects, and strontium ranelate which may have both bone and cartilage effects[62,63].

Other risk factors for pain in OA may be more amenable to modification. Psychological factors are well-recognized as being correlated with pain in OA, and the role of cognitive behavioral therapy is outlined elsewhere in this issue[39,64] (+REF). Specifically, some traits, such as catastrophizing, coping, and self-efficacy may be amenable to intervention[65–67]. While depression, anxiety, and negative affect, among others, have been associated with OA pain[42,68], the causal direction of such relationships is difficult to discern. Fluctuation in pain has been linked to fluctuation in psychological factors, but whether the pain influences the mood or *vice versa* is difficult to disentangle[69]. Although psychological factors can certainly contribute to a heightened pain experience, it is also possible that pain itself can contribute to poor mood. Such relationships can only be discerned from longitudinal studies, of which there are relatively few to date. For example, pain from OA contributed to functional limitations and fatigue, which in turn contributed to depressed mood and worse pain and function in one study evaluating these complex inter-relationships[70]. Functional brain imaging studies of OA also demonstrate an important role of affective and motivational aspects of pain[71,72] that should be addressed to improve effective management of OA-related pain. This is particularly important in light of the prevalence and impact of comorbid mood disorders on health outcomes.

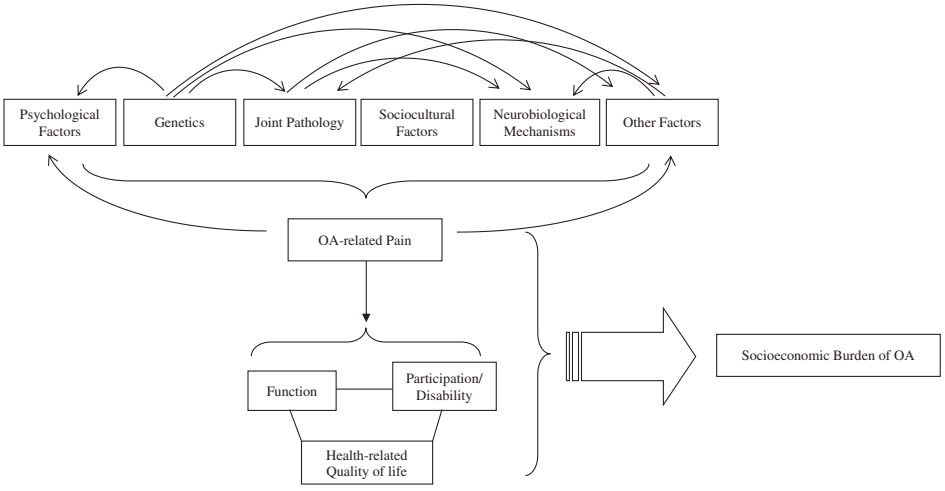

Fig. 1. Schematic illustrating the multifactorial nature of pain in OA, with complex inter-relationships between various risk factors, and the potential wide-ranging effects of OA pain.

Weight is a potential modifiable factor contributing not only to OA risk, but also to pain. The effect of obesity on pain may be two-fold. For the lower extremities, the effect of excess weights on symptoms may be due to mechanical loading. Increased relative fat mass in obesity may potentially contribute to pain symptoms related to elaboration of adipokines, although studies are conflicting in this regard[73,74]. While the mechanism by which obesity contributes to pain may not be clear, effects of altering weight on OA-related pain have been studied. Observational cohort data was used to demonstrate a lower risk of developing symptomatic knee OA among women who lost $\geq$5 kg[75]. Subsequent randomized trials have noted reductions in pain with $\sim$10% weight loss[76–78], with more substantial effects on pain reduction with greater weight loss[79]. Importantly, weight gain significantly increases pain, highlighting the dose–response relationship of change in weight with change in pain[80].

While not directly modifiable, there may be a genetic predisposition to development of chronic pain or experiencing greater pain severity that may provide insight into novel therapeutic targets. The availability of large cohort studies with standardized pain and X-ray data has facilitated genetic association studies to address such hypotheses. A functional polymorphism (Val158Met) in the *COMT* gene, which has been associated with pain sensitivity in other clinical conditions, was associated with hip OA-related pain in one cohort study[81], but has not yet been replicated in other cohorts. *TRPV1* and the PACE4 gene *PCSK6* were associated with pain in knee OA in two separate meta-analyses[82,83], while an association with a *SCN9* SNP could not be replicated[84]. A missense variant in *P2RX7*, a target identified through a genome-wide screen in mice with assessment of mechanical allodynia, has been associated with OA-related pain in one cohort[85]. Greater details of genetic determinants of pain can be found elsewhere in this issue (REF).

Another area that may provide potential therapeutic targets is related to risk factors that contribute to the transition from acute to chronic pain in OA, which at present is not well-understood. As noted in the qualitative work described above, there is a general progression of symptoms from the early stages of OA with activity-related (e.g., weight-bearing) symptoms that appear to be nociceptive in nature, to a more persistent constant pain that likely reflects other additional processes, such as neurobiological mechanisms. Tissue injury and/or inflammation, as may be seen in OA, leads to a decrease in the excitation threshold and an increase in responsiveness to suprathreshold stimuli of peripheral nociceptors, i.e., peripheral sensitization[86–88]. Noxious mechanical stimuli can then evoke exaggerated responses (primary hyperalgesia), and normally innocuous stimuli, such as movement of the joint through its normal range of motion, may evoke a pain response (allodynia). As a result of nociceptor activity after tissue injury or inflammation, a number of changes occur in the central nervous system. These include changes to dorsal horn transmission neuron receptors, leading the transmission neurons to become increasingly responsive to peripheral input (central sensitization), with reduction in the threshold for mechanically induced pain and an expansion of the receptive field of dorsal horn neurons (spatial summation)[89]. Radiating pain in OA likely reflects this latter phenomenon. Once established, central sensitization is maintained by low-level noxious and even non-nociceptive input from the periphery[90]. Such changes in the central nervous system are mainly responsible for the enhanced sensitivity to mechanical stimuli that develops outside the area of the injury (secondary hyperalgesia)[91–93].

Beyond the clinical observations of hyperalgesia, allodynia, and radiating pain that suggest a role for sensitization in OA-related pain, there are some experimental neurophysiologic findings that also support the presence of sensitization in OA. Persons with knee OA experience a greater intensity, duration, and area of hyperalgesia after intramuscular injection of hypertonic saline compared with controls[94]. Lidocaine injected into a painful OA knee resulted in pain reduction in both the injected knee and the untreated contralateral knee, supporting central pain modulation in OA[47]. Persons with knee OA have higher pain intensities compared with controls to the same level of pressure stimuli, as well as lower pressure pain thresholds[95]. Other studies have also documented lower pain thresholds in persons with OA compared with controls[96–98]. Temporal summation, a progressive increase in discharges of dorsal horn neurons in response to repetitive afferent stimulation thought to reflect central sensitization, is increased in persons with painful knee OA compared with age-matched healthy controls, and the degree of sensitization correlated with pain[99]. What pathologies of OA may contribute to peripheral and/or central sensitization, other risk factors for sensitization, and identification of the transition from appropriate nociceptive input to sensitization are important research questions that need to be addressed for improved understanding of pain mechanisms in OA. In addition, further development and validation of tools to assess sensitization will be necessary to support such research efforts[100].

Thus, there appears to be substantial opportunities to gain further insights into causes and contributors to pain in OA. Such insights in turn will provide opportunities for rational mechanism-based targeting of pain for more efficacious therapeutic management of OA patients.

Impact of OA-related pain

Because effective treatment for OA and its related pain is not available to date, and the disease can be present for decades, the public health impact of OA is substantial on an individual and societal level (Fig. 1). With the high prevalence of knee OA globally[101], not only is OA a leading cause of disability among older adults in the US[5,6], but it is among the top 10 causes of disability worldwide[101,102]. In recent estimates of global years lived in disability, musculoskeletal-related conditions ranked second, with low back pain, neck pain, and knee OA being the three most common such conditions, and knee OA itself ranked within the top 10 non-communicable diseases for global disability-adjusted life years (i.e., years of life lost and years lived with disability)[102].

Symptoms such as pain, stiffness, and gelling in OA have clear contributions to functional limitations in OA, with well-documented associations of pain severity with degree of functional limitation[103,104]. While most of the research focus to date has been on the knee or hip, symptomatic hand OA has important functional limitations, predominantly related to weaker grip strength and activities requiring precise pincer grip or power grip[16]. Nonetheless, a particular focus on lower extremity OA is warranted given the high prevalence of associated disability. In a longitudinal panel survey conducted by the US Census bureau, arthritis or rheumatism was the most commonly reported cause of disability, and difficulties related to lower extremity functioning or activities were the most commonly reported limitations among all respondents[105]. Specifically, the most common limitation was in walking three city blocks, which affected an estimated 22.5 million US adults, and difficulty with climbing stairs, affecting an estimated 21.7 million US adults[105]. While not all such individuals have symptomatic knee or hip OA, it is likely that OA accounts for a large proportion of these limitations. Based upon NHANES III data, among persons with OA, about 80% have some degree of movement limitation and 25% cannot perform major activities of daily living; 11% of adults with knee OA require help with personal care, and 14% require help with routine needs[9]. Symptomatic knee OA can have less obviously apparent effects on functioning as well. For example, persons with knee OA have slower walking speeds than those

without OA[106]. Further, those with symptomatic knee OA have a faster decline in gait speed over time than those with either knee OA alone or knee pain alone[107]. It is not surprising that knee pain also leads to restrictions in mobility outside of the house, impacting upon participation[108].

Symptomatic OA's economic impact is also substantial. Average direct medical charges related to OA care were estimated to be ~$2,600 per year per individual in 1997[109], and the total (i.e., direct and indirect) annual disease costs were estimated to be $5,700 per individual (USD, FY 2000)[110]. Those costs need to be considered in the context of the prevalence of the disease to appreciate the overall societal economic impact. OA as a primary diagnosis accounted for 11.25 million (22.3%) of all arthritis-related ambulatory medical care visits in 2006[111]. Further, arthritis-related conditions were the second most common reason for medical visits related to chronic conditions in 2005, second only to hypertension, which is asymptomatic[112]. In terms of inpatient costs, OA was the fifth most expensive condition treated in US hospitals in 2008, with a cost of ~$40 billion in total national hospital expenditures, comprising 3.5% of the national hospital bill, and accounting for 70% of all arthritis-related inpatient hospitalizations[111,113]. Much of those hospitalizations were related to joint replacement surgery. Pain is clearly among the main reasons for individuals seeking joint replacement. Knee replacement surgeries are one of the most commonly performed orthopedic procedures in the US, with ~50% of all joint arthoplasties performed on the knee, and 97% of those are performed for knee OA[111]. In 2004, 478,000 knee replacement surgeries were performed, representing a three-fold increase since 1991, with total hospitalization charges of $14.26 billion in 2004[111,114,115]. This increase exceeds expectations based upon overall population growth and increase in the proportion of the population that is elderly and/or obese. The demand for primary total knee replacement is expected to grow by 673% to 3.48 million procedures by 2030[116]. Adding to these costs is the increase in health care utilization in the 2 years preceding the surgery[117].

To appreciate the total economic burden of OA on society, indirect or productivity costs must also be examined. Productivity costs typically reflect costs due to lost productivity while being present at work, costs due to absence from work, and costs for compensation of household work by others[118]. Unfortunately, there are significant variations among indirect cost studies in OA regarding methodology, cost estimation, and cost presentation, limiting one's ability to determine the magnitude of OA's economic impact[119]. For example, in one review, indirect costs of OA per patient per year varied from $831 in Hong Kong to $12,789 in Canada (costs in 2006 USD)[119]. Considering the prevalence of OA, work-related OA costs have been estimated to range from $3.4 to $13.2 billion per year[120]. Estimates from 1999 indicate that adults with knee OA reported more than 13 days of lost work due to health issues[9]. Using a more recent large US employer benefits database, those with OA had an average of 63 days of absenteeism compared with 37 days among a matched comparator group, with mean total direct and indirect costs being two- to three-fold higher[121]. Similar findings were noted in a Swedish population-based cohort, in which those with physician-diagnosed knee OA had a two-fold increased risk of sick leave and 40–50% increased risk of disability pension compared with the general population[122]. Further, ~2% of all sick days in the population were attributable to knee OA. In a systematic literature review regarding work participation, occupational limitations and reduced work capacity or job effectiveness were reported more frequently in those with OA than by controls[123]. Aggregate annual absenteeism costs of OA were estimated to be ~$10 billion from the US Medical Expenditure Panel Survey, higher than many other major chronic diseases[124]. Taking into account both productivity costs and medical costs among adults with paid employment in a study from the Netherlands, the total economic burden of knee OA was estimated to be €871 per person, per month, with the majority of the costs being related to productivity[118]. Regardless of the methodologic differences, issues with cost estimation, and difficulties in comparing costs across studies, it is clear that OA has a tremendous economic impact that will only continue to grow with its rising prevalence.

Summary

OA is highly prevalent worldwide, with a tremendous symptomatic and economic global burden. Although a number of risk factors have been identified for pain in OA, the research focus to date has primarily been on structural targets. Pharmacologic treatment options remain limited and nonpharmacologic options are underutilized. An expansion of the research agenda to more fully explore pain mechanisms operational in OA is urgently needed to enable comprehensive mechanism-based pain management strategies in this prevalent, disabling, and costly disease.

Author contributions

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Conflict of interest

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