Title: How does hip osteoarthritis differ to knee osteoarthritis?

Michelle Hall[1†], Martin van der Esch[2,3†], Rana S Hinman[1], George Peat[4], Arjan de Zwart[2], Jonathan G Quicke[4], Jos Runhaar[5], Jesper Knoop[6], Marike van der Leeden[2,7], Mariëtte de Rooij[2], Ingrid Meulenbelt[8], Thea Vliet Vlieland[8], Willem F Lems[2,7], Melanie A Holden[4], Nadine E Foster[4,9], Kim L Bennell[1]

[†] Joint first co-authors

Affiliations:

1. Centre for Health Exercise and Sports Medicine, Department of Physiotherapy, School of Health Sciences, The University of Melbourne, Australia
2. Reade, center for rehabilitation and rheumatology, Amsterdam, The Netherlands
3. Center of Expertise Urban Vitality, University of Applied Sciences Amsterdam, The Netherlands
4. Primary Care Centre Versus Arthritis, School of Medicine, Keele University, UK
5. Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands
6. Vrije Universiteit Amsterdam, The Netherlands
7. Amsterdam UMC, location VUmc, department of rheumatology, Amsterdam, The Netherlands
8. Leiden UMC, Leiden, The Netherlands
9. STARS Research and Education Alliance, Surgical Treatment and Rehabilitation Service (STARS), The University of Queensland and Metro North Hospital and Health Service, Queensland, Australia

Corresponding Author:
Professor Kim Bennell
Centre for Health Exercise and Sports Medicine
Department of Physiotherapy
The University of Melbourne
Victoria, 3010, Australia
Tel: +61 3 8344 0556
Fax: +61 3 8344 4188
Email: k.bennell@unimelb.edu.au

Running title: differences between hip and knee osteoarthritis

Summary

Hip and knee osteoarthritis are leading causes of global disability. Most research to date has focused on the knee, with results often extrapolated to the hip, and this extends to treatment recommendations in clinical guidelines. Extrapolating results from research on knee OA may limit our understanding of disease characteristics specific to hip OA, thereby constraining development and implementation of effective treatments. This review highlights differences between hip and knee OA with respect to prevalence, prognosis, epigenetics, pathophysiology, anatomical and biomechanical factors, clinical presentation, pain and non-surgical treatment recommendations and management.

Keywords: hip osteoarthritis; knee osteoarthritis; non-surgical treatments; exercise

Abbreviations

CD: cluster of differentiation

CI: confidence interval

COMP: cartilage oligomeric matrix protein

CrI: credibility interval

DNA: deoxyribonucleic acid

EGF: epidermal growth factor

ES: effect size

FGF_2: fibroblast growth factor 2

IL: interleukin

IP: interferon gamma-induced protein

OA: osteoarthritis

MCP: monocyte chemoattractant protein

MDC: macrophage-derived chemokine

MIP: macrophage inflammatory protein

RNA: ribonucleic acid

SMD: standardised mean difference

TNF: tumor necrosis factor

VI: six

Osteoarthritis (OA) of the hip and knee is a leading cause of global disability [1] for which there are limited efficacious non-surgical treatment options [2-6]. The increase in rates of hip and knee joint replacement for OA [7, 8] highlights the urgent need for effective non-surgical treatments. Most research has focused on the knee or mixed populations of hip and knee OA, the results of which have often been extrapolated to the hip, including treatment recommendations in clinical guidelines [2, 5]. This may limit our understanding of disease characteristics specific to hip OA and lead to questionable external validity of treatment responses, thereby constraining the development and implementation of effective treatments for hip OA. The purpose of this review is to highlight potential differences between hip OA and knee OA. Areas covered include prevalence, prognosis, epigenetics, pathophysiology, anatomical and biomechanical factors, clinical presentation pain, clinical management recommendations and current practice.

PubMed and Google Scholar were searched for articles in the English language directly comparing hip and knee OA using search terms ‘hip OA versus knee OA; ‘differenc* between hip OA knee OA’ and ‘compar* hip OA and knee OA’. The reference lists and citations of publications directly comparing hip and knee OA were also reviewed. As expected, few studies directly compare people with hip and knee OA. The conditions were typically investigated either separately, or in mixed samples of people with both hip and knee OA. Although we aimed to focus our narrative review on studies directly comparing hip and knee OA, in their absence, we used evidence from systematic review and meta-analyses on people with hip and/or knee OA. For topics not addressed by direct comparison or synthesised in meta-analyses, we utilised results of selected experimental, observational and qualitative reports.

Prevalence

Symptomatic radiographically confirmed OA is less prevalent at the hip than the knee, affecting approximately 10% and 16% in a population sample aged 45 years and older, respectively [9, 10]. However, modelled estimates from the Global Burden of Disease initiative suggest an even greater difference in the number of prevalent cases of hip and knee OA globally [11]. A meta-analysis determined that the prevalence of hip OA is similar between men and women, but that knee OA affects more women than men [12]. Hip OA is less common among Chinese than US White women whereas knee OA is more common in Chinese than US White women [13]. In contrast to knee OA, hip OA does not appear more prevalent among African Americans more than White although racial differences may exist for specific features such as osteophyte formation [9, 10, 13]. It is also important to recognise that many people have both hip and knee OA. A large study (n=16,222) of individuals >55 years found that multiple-site joint problems are much more common than single joint problems, with only one in eight people who reported joint problems experiencing problems in a single joint [14]. Hence research evaluating OA treatments in populations with concurrent hip and knee OA are arguably also very relevant depending on the research question.

Prognosis

Despite fluctuation in symptoms, the radiographic and symptomatic course over 10 years is relatively stable in early hip and knee OA and comparable between the joints [15]. Systematic reviews of trajectory-based studies have been unable to determine conclusions to the course of pain and physical function in people with hip OA [16] or knee OA [17] due to heterogeneity across studies and within populations. However, differences in risk factors associated with symptomatic and radiographic disease progression potentially exist between

hip and knee OA according to systematic reviews (Table 1) [18-21]. Other studies not included in the systematic review [24] report an association between additional anatomical features (e.g. cam deformity) and radiographic hip OA disease progression [22]. Associations between bone marrow lesions and OA progression, are joint specific. Specifically, large bone marrow lesions located in acetabular and femoral head are associated with hip OA pain, where as an increase of 2 or more in whole-organ magnetic imaging scoring bone marrow lesion is associated with worsening of knee OA pain [21]. Of note is that obesity, a strong risk factor for clinical knee OA progression, has generally not been found to be a strong risk factor for symptomatic or radiographic hip OA disease progression. This epidemiological evidence suggests that hip and knee OA have at least in part different pathogenic progresses, that should be considered in the development of joint-specific treatments.

The long-term prognosis for hip OA differs from knee OA. People with hip OA are more likely to opt for joint replacement earlier (hazard ratio 1.86, 95% CI 1.19 to 1.23) [23], and are more likely to be male, younger and have a lower body mass index than those undergoing knee replacement according to the Australian Orthopaedic Association National Joint Replacement Registry [21]. Reasons for these differences are unclear but less time to hip replacement surgery may suggest a shorter window of opportunity for non-surgical treatments to satisfactorily improve symptoms. One possible explanation for a shorter time to surgery for hip OA may relate to the phenomenon of ‘forgotten hip’ (i.e. perception that replaced hip is natural) [24] and high patient satisfaction with hip replacement (93-98%), which is much greater compared to satisfaction with knee replacement (76-80%) [25, 26]. However, despite greater patient satisfaction with hip replacement, the revision burden for hip replacement is greater than the revision burden for knee replacement [27, 28]. The

differences in the long-term prognosis between hip and knee OA provide further evidence for joint-specific treatment implementation.

Epigenetics

Although there are genetic loci relevant to OA across multiple joints [29], there is increasing evidence that deviation in cellular control mechanisms associated with OA progression are different in hip and knee joints. Chondrocytes, as postmitotic cells, are highly dependent on such epigenetic control mechanisms to regulate dynamic changes in gene expression in response to environmental cues such as mechanical stress, non-beneficial metabolic factors or disease process. Studies on differences in epigenetic regulation as a function of either joint site or OA pathophysiology have focussed on a variety of epigenetic mechanisms; DNA methylation [30, 31], histone modifications [32], and microRNAs [33] and long non-coding RNAs [34].

Genome wide profiles of DNA methylation have revealed distinct epigenetic landscapes of knee and hip articular cartilage, highlighting large differentially methylated regions at Hox-genes, a subset of homebox genes [30]. Given that HOX-genes were also found to regulate regenerative propensity of neural crest cells [35], differences in regenerative capacities of knee and hip articular chondrocytes may exist [30]. Another level of epigenetically regulated gene transcription found to be involved in pathological processes are microRNAs, which affect gene translation by interfering with mRNA. By integrating microRNA with gene expression data of preserved and lesioned OA articular cartilage, a miRNA interactome of the OA pathophysiological process was uncovered [33]. Upon screening for joint-specific differentially expressed miRNAs, a clear difference in overall mean level and number of differentially expressed miRNAs in knee and hip articular cartilage was observed.

Particularly notable was the exclusive hip miRNA miR-451a that was highly significantly differentially expressed between preserved and lesioned hip OA cartilage, yet not differentially expressed in knees [33]. Targeting such a unique dysfunctional miRNA–mRNA interaction fulfils an important joint-specific therapeutic opportunity [36, 37]. Therapeutic strategies that focus on early OA should consider these inherent mechanisms that control and maintain healthy joint tissue homeostasis in a joint-specific manner.

Pathophysiology

Osteoarthritis is typically seen as a 'whole joint disease' such that all of the structures of the joint including the cartilage, bone and synovium and surrounding muscles can be affected by the disease [38]. There is a complicated interaction between both systemic and local inflammation, and mechanical stress is considered to cause an imbalance between destruction and repair, ultimately leading to joint failure [39-41]. In animal studies, evidence suggests that the molecular pathophysiology differs between hip and knee OA [42, 43]. In collagen VI knock out mice, hip OA is accelerated with aging [42] while cartilage degeneration is delayed at the knee joint [43]. The implications of these differences require further understanding, especially given that collagen VI exerts several key roles including unique biomechanical contributions [44].

Emerging cross-sectional studies directly comparing hip and knee OA in humans suggest differences in inflammatory processes as measured in the serum [45] and synovium [46]. Distinct serum cytokine profiles were found in which EGF, FGF_2, MCP_3, $MIP_1\alpha$, and IL8 were differentially expressed between people with hip and knee OA [45]. Interestingly, there were significant associations between hip OA pain and IL6, MDC and IP10, but these markers did not differ between hip and knee OA [45]. A large meta-analysis of 3,582

individuals found an association between serum levels of COMP and incidence of hip and knee OA [47]. However, preliminary evidence suggests that serum COMP may be related to joint-specific symptoms [48]. In people with symptoms of hip and knee OA, but not radiographic OA, a significant association was observed between higher serum COMP and hip-related symptoms, but not knee-related symptoms [48]. Another more recent study observed a 4-fold increased presence of macrophages (e.g. $CD14^{+}$) in the synovial membrane of knee OA samples compared to hip OA, whereas higher concentration of several markers including, but not limited to IL4, IL10, TNFα were found in isolates from synovial membrane from hip OA compared to knee OA [46]. Taken together, some studies support differences in the cellular and molecular pathophysiology of OA at the hip and knee joint that, although require replication in future research, may lead to the novel development of joint-specific OA treatments.

Anatomical and biomechanical factors

The hip and knee joints are the largest joints in the body with notable anatomical differences [49] that may influence the development and effectiveness of biomechanical treatments. Specifically, the hip is a ball and socket joint, and the knee is a more complex bicondylar hinge joint [49]. The anatomical differences between the hip and knee joint are likely to underpin why malalignment is risk factor for knee OA [18], but not hip OA. Osteoarthritis is considered in part a mechanical disease [40, 50] and biomechanical strategies to improve symptoms and slow disease progression are a highly valued research priority for OA [51]. Joint loads are often indirectly assessed during gait analysis, with external moments most often reported. In contrast to knee OA [52-54], no evidence has been found to support a longitudinal association between parameters of hip joint loading and disease progression [55, 56]. Hence, there are few hip OA treatments targeting hip joint loading, which is in stark

contrast to the abundance of biomechanical interventions (e.g. lateral wedges, gait retraining, knee bracing) for knee OA.

To our knowledge, studies that have directly compared gait biomechanics between people with hip and knee OA are sparse and limited to the sagittal plane [57, 58]. Kinematics differences include greater knee flexion and less hip flexion in hip OA compared to knee OA [57, 58]. Systematic reviews and meta-analyses demonstrate that external joint moments differ in people with hip and knee OA compared to healthy controls. Relative to controls, hip joint moments in the frontal and sagittal plane are lower in hip OA [55], while knee joint moments in the frontal plane are higher in knee OA [54]. Lower hip moments in hip OA, are thought to reflect an adaptive strategy to alleviate force from the painful osteoarthritic joint [59] consistent with the intense description of the pain experience described by people with hip OA [60]. In contrast to hip OA, frontal plane malalignment is a key driver of higher knee joint loads in knee OA [61, 62]. The debatable agreement between external joint moment and internal joint contact forces [63] perhaps questions the validity of external joint moments. However, cross-sectional studies using electromyography-informed neuromusculoskeletal models which are thought to better reflect *in-vivo* knee joint loads [64, 65] also observed lower hip joint contact forces in hip OA [61] and higher knee joint contact forces in knee OA [66]. Overall, the relevance of treatments targeting hip joint loading to manage hip OA is uncertain given the notable lack of longitudinal biomechanical studies in hip OA.

Clinical presentation

People with hip OA tend to be younger (60.4 years) than people with knee OA (66.3 years) [67] and have shorter duration of symptoms at the time of presentation (2.7 years, [95% CI 1.6, 5.6 years]) compared to people with knee OA (3.9 years, [95% CI 2, 8 years]) [23].

Although it is unclear why symptom duration may be shorter with hip OA, other differences in clinical presentation of hip OA and knee OA may provide insights into joint-specific treatment targets such as restricted range of motion and joint instability. Restricted joint range of motion is typically more problematic with hip OA compared to knee OA [68] such that clinical assessment and diagnosis of OA places attention on restricted range of motion [69, 70] to a much greater extent at the hip than the knee. In contrast, restricted knee flexion and extension does not typically play a role in the clinical diagnosis of knee OA [70]. Joint instability, described as the feeling of buckling or giving way, is frequently reported in knee OA, but not often in people with hip OA [71, 72]. Hip joint instability is perhaps less likely to occur than knee joint instability due to the anatomical structure of the hip joint [73]. In contrast, the knee joint relies on ligaments for stability [49] and anterior cruciate ligament injury is among the most common of knee injuries and is a potent risk factor for knee OA [74] which also may contribute to knee instability in knee OA [75]. Thus, flexibility exercises may be more effective for hip OA, whereas enhancing neuromuscular control of the knee musculature with or without biomechanical intervention (e.g. bracing) may be more beneficial for knee OA.

Pain

People with hip and knee OA experience joint pain and difficulty with activities of daily living. Qualitative research provides insights into how the experience of pain differs between hip and knee OA [60, 76]. People with hip and knee OA typically describe their pain as a dull, aching pain that becomes constant over time and punctuated increasingly with short episodes of a more intense, often unpredictable, emotionally draining pain. In contrast to knee OA, people with hip OA described their pain as abrupt, rapidly progressing from mild to severe pain, ‘intense’ (such as an ice-pick, pickaxe, spike, paralysing) and more often

compare their pain to other extremely painful conditions such as childbirth. In expressing their experience of OA, people with hip OA are concerned with sidedness (e.g. lying down) and groin pain (e.g. sexual activity), whereas people with knee OA focus on stairs, body weight and joint stiffness [76]. The difference between experience of hip and knee pain suggests that treatments should be approached accordingly to affected joint.

In addition to differences in the pain experience, there is also evidence to suggest that methods of coping with OA pain differ in people with hip OA compared to knee OA. A large cross-sectional study found that passive pain coping scores were significantly lower in people with hip OA (n=1,553) compared to knee OA (n=2,781) [77]. This observation was found when adjusting for body mass index, age and duration of OA and suggests that people with hip OA engage less in passive pain coping strategies (e.g. worrying, resting, retreating) than those with knee OA. Interestingly, a longitudinal study determined that the passive pain coping strategy of resting predicts greater disability in knee OA (n=119), but not in hip OA (n=71) [78]. Understanding differences in pain experiences, and how patients cope with joint-specific OA symptoms could help in tailoring biopsychosocial interventions to patients who have symptomatic hip or knee OA.

Efforts are underway to better understand OA pain including investigations into neuropathic pain. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system [79]. Using self-report questionnaires, a meta-analysis determined that the prevalence of possible neuropathic-like pain is potentially less prevalent in hip OA (29%) compared to knee OA (40%) with a difference of 11% (95% CI 0-22%) [80]. A cross-sectional study (n=843) suggests that neuropathic pain may be dependent on OA joint and sex. In patients with end-stage OA, women with hip OA had significantly fewer neuropathic-

like symptoms compared to women with knee OA, but such differences were not apparent in men [81]. The implications of neuropathic-like symptoms are still emerging and may differ according to site of OA [82]. Cross-sectional evidence based on separate joint analyses suggests that the presence of neuropathic-like symptoms is associated with reduced pain-related quality of life in hip OA (n=117) only (change in RAND-36 bodily pain: 6.8 points). In contrast, knee OA (n=138) neuropathic-like symptoms was only associated with physical dysfunction (change in RAND-36 physical function score 6.8 points) [82]. Collectively, these data suggest that mechanisms of pain may be joint-dependent and have joint-specific implications on outcomes.

Brain-imaging studies are emerging to better understand neuropathic mechanisms of pain in OA [83-86]. Gray matter, a major component of the central nervous system, is known to be altered in people with chronic pain compared to healthy controls [87]. A recent cross-sectional investigation that controlled for age and sex statistically, found less gray matter in the anterior cingulate cortex of people awaiting hip replacement (n=24) compared to people awaiting knee replacement for OA (n=91) [85]. The anterior cingulate cortex is responsible for functions including the registration of pain [88] and emotional reaction to pain [89]. Although gray matter indices indicate morphologic brain differences between hip and knee OA, the clinical implication remains uncertain as the gray matter alterations were poorly associated with clinical symptoms [84].

Management recommendations and current practice

Clinical guidelines [2-5] for the management of hip and knee OA recommend non-pharmacological interventions prior to pharmacological and surgical options. However, there is a paucity of high-quality clinical trials evaluating non-surgical treatments for hip OA [2, 5]

(Figure 1). Accordingly, several clinical practice guidelines have formed some treatment recommendations for hip OA based on evidence from clinical trials in knee OA or mixed populations of hip and knee OA [2, 3, 5]. However, due to potential differences in treatment outcomes, the Osteoarthritis Research Society International recommends that efficacy trials should be conducted in populations that have a single target osteoarthritic joint [90].

The following two sections outline differences in treatment recommendations between hip and knee OA and differences in current clinical practice to highlight areas of improvement with respect to implementation of recommended treatments.

Non-pharmacological management

Education and exercise therapy are core treatments consistently recommended for both hip and knee OA [2, 3, 5, 6]. Weight loss, if appropriate, is also consistently recommended as a core treatment for knee OA [2, 3, 5, 6] but inconsistently recommended for hip OA [2, 3, 5, 6] due to absence of weight-loss trials specifically with people with hip OA [2]. Other treatment options recommended for management of knee OA include bracing and kinesiotaping, but these treatment options are not recommended for hip OA [5].

Despite the consistent recommendation for exercise across guidelines, people with hip and knee OA are more likely to receive a referral to an orthopaedic surgeon than to a physiotherapist [91]. In Australian general practice, there are no differences between knee and hip OA in the frequency of referral to a physiotherapist or dietitian/nutritionist [91]. A cross-sectional survey suggests a greater proportion of people with knee OA compared to hip OA engage with efforts to lose weight, strengthening exercise, heat/cold treatments and walking aids [92]. Hence despite no differences in referral rates between the joints, people

with hip OA are perhaps less likely to engage in non-pharmacological treatments compared to knee OA.

Pharmacological management

There are several differences in recommendations by clinical guidelines for pharmacological treatments in management of hip and knee OA. Topical NSAIDs are strongly recommended for knee OA [3-5], but with no evidence from clinical trials in hip OA, clinical practice guidelines from major societies do not make a recommendation for or against the use of topical NSAIDs for hip OA [2, 5]. Duloxetine is recommended for knee OA [2, 5] but recommendations for use in hip OA are inconsistent, with some guidelines recommending for [5] and others against [2] its use in the absence of clinical trials evidence in hip OA. Whilst recommendations for [2] and against [4, 5] the use of hyaluronic acid injection for knee OA are inconsistent across clinical guidelines, recommendations against the use of hyaluronic acid injection are consistent across guidelines for management of hip OA [2, 4, 5].

There are some differences in the pharmacological management of hip and knee in general practice. In the UK, patients with hip OA are more likely to use painkillers for their pain than knee OA [93]. Somewhat similarly, patients with hip OA in Australia were prescribed medications more frequently than people with knee OA, with prescriptions for opioids in particular more frequent for hip OA (rate per 100 hip OA problems managed 25.6 [95%CI 22.8 to 28.4]) than knee OA (rate per 100 knee OA problems managed 14.9 [95% CI 13.7 to 16.2]) [91]. Although not recommended in clinical practice guidelines for hip or knee OA management [2, 4, 5], glucosamine is more frequently prescribed for knee OA than hip OA [91]. In contrast, albeit indirectly, there were no differences in consumption of analgesics by people with early hip or knee OA in the Netherlands [94]. General practitioners administered

joint injections more frequently for knee OA than hip OA [91]. Other studies have reported on health care use of hip and knee OA combined but have not presented the data for hip and knee OA separately [95].

Health service utilisation

There are some differences in health service utilisation between hip and knee OA. Imaging is typically not required to make an OA diagnosis [96, 97]. However, in Australian general practice, referrals for diagnostic radiology, that include x-ray but exclude magnetic resonance imaging and ultrasound, is more frequent for hip OA (rate per 100 hip OA problems managed 30.0 [95% CI 26.8-33.2] 22.0 [95%CI 20.6-23.3]) compared to knee OA (rate per 100 knee OA problems managed 22.0 [95%CI 20.6-23.3] [91]. The higher rates of referrals for diagnostic radiology at the hip joint may relate to the complexity of hip joint pain. Multiple hip conditions including OA, gluteal tendinopathy [98] and femoral acetabular impingement syndrome [99] are common and can often co-exist [100], although it remains unsubstantiated whether a radiological-based diagnosis is necessary to improve outcomes. Furthermore, the revision burden for hip replacement is greater than the revision burden for knee replacement. Based on data from the US Nationwide Inpatient Sample (n=537,575), health care utilisation tends to be greater for revision of hip replacement with respect to length of hospital stay (mean [SD]: 5.8 [14] days and 4.8 [10.5] for hip and knee respectively) and hospital costs (mean USD [SD]: $24,697 [$40,489] and $23,130 [$36,643] for hip and knee respectively) [27]. Although differences in health service utilisation may be country-specific, these observations point to underlying differences in disease characteristics between hip and knee OA that remain largely under-investigated.

Summary

This review highlights differences between hip and knee OA with respect to prevalence, prognosis, epigenetics, pathophysiology, anatomical and biomechanical factors, clinical presentation, pain and clinical practice recommendations and current practice (Table 2). It should be strongly noted that there is much less research into hip OA compared to knee OA. Hence, much remains unknown about how similar or how different hip and knee OA actually are. The notable lack of clinical trials in hip OA compared to knee OA may be due to the greater prevalence of knee OA, reluctance of research funders to fund trials for a clinical condition perceived to be similar, and because of the historical approach of generalising findings from knee OA to hip OA. Differences between hip and knee OA should be contemplated when considering the mechanisms underpinning treatment effects and highlight the need to assess treatments specific to the osteoarthritic joint as recommended [90] either by conducting single-joint trials or adequately powering trials to conduct analysis by affected joint. In conclusion, alongside 'pragmatic studies' addressing complex needs and shared treatment mechanisms in heterogenous populations such as those with hip and knee OA, there is a need for more hip OA specific research addressing distinct descriptive, predictive, causative and interventions questions.

Author contributions

M vdE, KLB and RSH conceived the idea for the review. All authors were involved in drafting the article or revising it critically for intellectual content, and all authors approved the final paper.

Competing interests

None of the authors have any competing interests to declare.

Role of funding sources

MH is supported by a National Health and Medical Research Council (NHMRC) Investigator Grant Emerging Leader 1 (#1172928). RSH is supported by a NHMRC Senior Research Fellowship (#1154217). KLB is supported by a NHMRC Investigator Grant Leadership 2 (#1174431). JQ is part- funded by an NIHR CRN West Midlands Research Scholarship and part funded by the Haywood Foundation. The views expressed are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health and Social Care. Funding sources had no role in study design, data design, data analysis, data interpretation or writing the manuscript.

Figure Legend

Figure 1 Standardised mean difference (95% confidence intervals) in pain from trials that informed the 2019 Osteoarthritis Research Society clinical guidelines for hip and osteoarthritis management. NSAIDS: non-steroidal anti-inflammatory drugs

REFERENCES

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014; 73: 1323-1330. doi: 10.1136/annrheumdis-2013-204763.
2. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27: 1578-1589. doi: 10.1016/j.joca.2019.06.011.
3. Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013; 72: 1125-1135. doi: 10.1136/annrheumdis-2012-202745.
4. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 2013; 21: 571-576. doi: 10.5435/JAAOS-21-09-571.
5. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol 2020; 72: 220-233. doi: 10.1002/acr.24131.
6. National Clinical Guideline Centre. Osteoarthritis. Care and management in adults. National Institute for Health and Care in Excellence. 2014.
7. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, et al. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. Osteoarthritis Cartilage 2017; 25: 455-461. doi: 10.1016/j.joca.2016.11.005.

8. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, et al. Lifetime Risk of Primary Total Hip Replacement Surgery for Osteoarthritis From 2003 to 2013: A Multinational Analysis Using National Registry Data. Arthritis Care Res (Hoboken) 2017; 69: 1659-1667. doi: 10.1002/acr.23197.

9. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007; 34: 172-180. doi: 10.3899/jrheum.080677.

10. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2009; 36: 809-815. doi: 10.3899/jrheum.080677.

11. Vos T LS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1204-1222. doi: 10.1016/S0140-6736(20)30925-9.

12. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005; 13: 769-781. doi: 10.1016/j.joca.2005.04.014.

13. Allen KD. Racial and ethnic disparities in osteoarthritis phenotypes. Curr Opin Rheumatol 2010; 22: 528-532. doi: 10.1097/BOR.0b013e32833b1b6f.

14. Keenan AM, Tennant A, Fear J, Emery P, Conaghan PG. Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. Arthritis Rheum 2006; 55: 757-764. doi: 10.1002/art.22239.

15. Schiphof D, Runhaar J, Waarsing JH, van Spil WE, van Middelkoop M, Bierma-Zeinstra SMA. The clinical and radiographic course of early knee and hip osteoarthritis over 10 years in CHECK (Cohort Hip and Cohort Knee). Osteoarthritis Cartilage 2019; 27: 1491-1500. doi: 10.1016/j.joca.2019.06.002.

16. de Rooij M, van der Leeden M, Heymans MW, Holla JF, Häkkinen A, Lems WF, et al. Course and predictors of pain and physical functioning in patients with hip osteoarthritis: Systematic review and meta-analysis. J Rehabil Med 2016; 48: 245-252. doi: 10.2340/16501977-2057.

17. de Rooij M, van der Leeden M, Heymans MW, Holla JF, Häkkinen A, Lems WF, et al. Prognosis of pain and physical functioning in patients with knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2016; 68: 481-492. doi: 10.2340/16501977-2057.

18. Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SM. What are the prognostic factors for radiographic progression of knee osteoarthritis? a meta-analysis. Clin Orthop Relat Res 2015; 473: 2969-2989. doi: 10.1007/s11999-015-4349-z.

19. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SMA. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther 2015; 17: 152. doi: 10.1186/s13075-015-0670-x.

20. Teirlinck CH, Dorleijn DMJ, Bos PK, Rijkels-Otters JBM, Bierma-Zeinstra SMA, Luijsterburg PAJ. Prognostic factors for progression of osteoarthritis of the hip: a systematic review. Arthritis Res Ther 2019; 21: 192. doi: 10.1186/s13075-019-1969-9

21. Sandhar S, Smith TO, Toor K, Howe F, Sofat N. Risk factors for pain and functional impairment in people with knee and hip osteoarthritis: a systematic review and meta-analysis. BMJ Open 2020; 10: e038720. doi: 10.1136/bmjopen-2020-038720.

22. Nelson AE, Stiller JL, Shi XA, Leyland KM, Renner JB, Schwartz TA, et al. Measures of hip morphology are related to development of worsening radiographic hip osteoarthritis over 6 to 13 year follow-up: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage 2016; 24: 443-450. doi: 10.1016/j.joca.2015.10.007.

23. Dabare C, Le Marshall K, Leung A, Page CJ, Choong PF, Lim KK. Differences in presentation, progression and rates of arthroplasty between hip and knee osteoarthritis: Observations from an osteoarthritis cohort study-a clear role for conservative management. Int J Rheum Dis 2017; 20: 1350-1360. doi: 10.1111/1756-185X.13083.

24. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The "forgotten joint" as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome measure. J Arthroplasty 2012; 27: 430-436.e431. doi: 10.1016/j.arth.2011.06.035.

25. Okafor L, Chen AF. Patient satisfaction and total hip arthroplasty: a review. Arthroplasty 2019; 1: 6. doi: 10.1186/s42836-019-0007-3.

26. Varacallo M, Chakravarty R, Denehy K, Star A. Joint perception and patient perceived satisfaction after total hip and knee arthroplasty in the American population. J Orthop 2018; 15: 495-499. doi: 10.1016/j.jor.2018.03.018.

27. Bozic KJ, Kamath AF, Ong K, Lau E, Kurtz S, Chan V, et al. Comparative epidemiology of revision arthroplasty: failed THA poses greater clinical and economic burdens than failed TKA. Clin Orthop Relat Res 2015; 473: 2131-2138. doi: 10.1007/s11999-014-4078-8.

28. McGrory BJ, Etkin CD, Lewallen DG. Comparing contemporary revision burden among hip and knee joint replacement registries. Arthroplast Today 2016; 2: 83-86. doi: 10.1016/j.artd.2016.04.003.

29. Reynard LN, Barter MJ. Osteoarthritis year in review 2019: genetics, genomics and epigenetics. Osteoarthritis Cartilage 2020; 28: 275-284. doi: 10.1016/j.joca.2019.11.010.

30. den Hollander W, Ramos YF, Bos SD, Bomer N, van der Breggen R, Lakenberg N, et al. Knee and hip articular cartilage have distinct epigenomic landscapes: implications for future cartilage regeneration approaches. Ann Rheum Dis 2014; 73: 2208-2212. doi: 10.1136/annrheumdis-2014-205980.

31. Rushton MD, Young DA, Loughlin J, Reynard LN. Differential DNA methylation and expression of inflammatory and zinc transporter genes defines subgroups of osteoarthritic hip patients. Ann Rheum Dis 2015; 74: 1778-1782. doi: 10.1136/annrheumdis-2014-206752.

32. Cheung K, Barter MJ, Falk J, Proctor CJ, Reynard LN, Young DA. Histone ChIP-Seq identifies differential enhancer usage during chondrogenesis as critical for defining cell-type specificity. FASEB J 2020; 34: 5317-5331. doi: 10.1096/fj.201902061RR.

33. Coutinho de Almeida R, Ramos YFM, Mahfouz A, den Hollander W, Lakenberg N, Houtman E, et al. RNA sequencing data integration reveals an miRNA interactome of osteoarthritis cartilage. Ann Rheum Dis 2019; 78: 270-277.

34. van Hoolwerff M, Metselaar PI, Tuerlings M, Suchiman HED, Lakenberg N, Ramos YFM, et al. Elucidating epigenetic regulation by identifying functional cis-acting long noncoding RNAs and their targets in osteoarthritic articular cartilage. Arthritis Rheumatol 2020; 72: 1845-1854. doi: 10.1002/art.41396.

35. Le Douarin NM, Creuzet S, Couly G, Dupin E. Neural crest cell plasticity and its limits. Development 2004; 131: 4637-4650. doi: 10.1242/dev.01350.

553 36. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the
554 management of cancer and other diseases. Nat Rev Drug Discov 2017; 16: 203-222.
555 doi: 10.1038/nrd.2016.246.
556 37. Vicente R, Noël D, Pers YM, Apparailly F, Jorgensen C. Deregulation and
557 therapeutic potential of microRNAs in arthritic diseases. Nat Rev Rheumatol 2016;
558 12: 211-220. doi: 10.1038/nrrheum.2015.162.
559 38. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized
560 definitions of osteoarthritis and risk stratification for clinical trials and clinical use.
561 Osteoarthritis Cartilage 2015; 23: 1233-1241. doi: 10.1016/j.joca.2015.03.036.
562 39. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance
563 for clinical practice. The Lancet 2011; 377: 2115-2126. doi: 10.1016/S0140-
564 6736(11)60243-2.
565 40. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019; 393: 1745-1759. doi:
566 10.1016/S0140-6736(19)30417-9.
567 41. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-
568 grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev
569 Rheumatol 2016; 12: 580-592. doi: 10.1038/nrrheum.2016.136.
570 42. Alexopoulos LG, Youn I, Bonaldo P, Guilak F. Developmental and osteoarthritic
571 changes in Col6a1-knockout mice: biomechanics of type VI collagen in the cartilage
572 pericellular matrix. Arthritis Rheum 2009; 60: 771-779. doi: 10.1002/art.24293.
573 43. Christensen SE, Coles JM, Zelenski NA, Furman BD, Leddy HA, Zauscher S, et al.
574 Altered trabecular bone structure and delayed cartilage degeneration in the knees of
575 collagen VI null mice. PloS One 2012; 7: e33397-e33397. doi:
576 10.1371/journal.pone.0033397.

44. Cescon M, Gattazzo F, Chen P, Bonaldo P. Collagen VI at a glance. J of Cell Sci 2015; 128: 3525-3531. doi: 10.1242/jcs.169748.

45. Ren G, Lutz I, Railton P, Wiley JP, McAllister J, Powell J, et al. Serum and synovial fluid cytokine profiling in hip osteoarthritis: distinct from knee osteoarthritis and correlated with pain. BMC Musculoskelet Disord 2018; 19: 39. doi: 10.1186/s12891-018-1955-4.

46. Grieshaber-Bouyer R, Kämmerer T, Rosshirt N, Nees TA, Koniezke P, Tripel E, et al. Divergent mononuclear cell participation and cytokine release profiles define hip and knee osteoarthritis. J Clin Med 2019; 8: 1631. doi: 10.3390/jcm8101631.

47. Valdes AM, Meulenbelt I, Chassaing E, Arden NK, Bierma-Zeinstra S, Hart D, et al. Large scale meta-analysis of urinary C-terminal telopeptide, serum cartilage oligomeric protein and matrix metalloprotease degraded type II collagen and their role in prevalence, incidence and progression of osteoarthritis. Osteoarthritis Cartilage 2014; 22: 683-689. doi: 10.1016/j.joca.2014.02.007.

48. Dragomir AD, Kraus VB, Renner JB, Luta G, Clark A, Vilim V, et al. Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. Osteoarthritis Cartilage 2002; 10: 687-691. doi: 10.1053/joca.2002.0816.

49. Palastanga N, Soames R. Anatomy and Human Movement. 6th Edition, Churchill Livingstone 2011.

50. Cicuttini FM, Wluka AE. Osteoarthritis: Is OA a mechanical or systemic disease? Nat Rev Rheumatol 2014; 10: 515-516. doi: 10.1038/nrrheum.2014.114.

51. Gierisch JM, Myers ER, Schmit KM, McCrory DC, Coeytaux RR, Crowley MJ, et al. Prioritization of patient-centered comparative effectiveness research for osteoarthritis. Ann Intern Med 2014; 160: 836-841. doi: 10.7326/M14-0318.

52. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, et al. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1099-1106. doi: 10.1016/j.joca.2015.02.005.

53. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis Cartilage 2014; 22: 1833-1839. doi: 10.1016/j.joca.2014.08.009.

54. Henriksen M, Creaby MW, Lund H, Juhl C, Christensen R. Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials. BMJ Open 2014; 4: e005368. doi: 10.1136/bmjopen-2014-005368.

55. Kumar D, Wyatt C, Lee S, Okazaki N, Chiba K, Link TM, et al. Sagittal plane walking patterns are related to MRI changes over 18-months in people with and without mild-moderate hip osteoarthritis. J Orthop Res 2018; 36: 1472-1477. doi: 10.1002/jor.23763.

56. Tateuchi H, Koyama Y, Akiyama H, Goto K, So K, Kuroda Y, et al. Daily cumulative hip moment is associated with radiographic progression of secondary hip osteoarthritis. Osteoarthritis Cartilage 2017; 25: 1291-1298. doi: 10.1016/j.joca.2017.02.049.

57. Nüesch C, Ismailidis P, Koch D, Pagenstert G, Ilchmann T, Eckardt A, et al. Assessing Site Specificity of Osteoarthritic Gait Kinematics with Wearable Sensors and Their Association with Patient Reported Outcome Measures (PROMs): Knee versus Hip Osteoarthritis. Sensors 2021; 21: 5363. doi: 10.3390/s21165363.

58. Schmitt D, Vap A, Queen RM. Effect of end-stage hip, knee, and ankle osteoarthritis on walking mechanics. Gait Posture 2015; 42: 373-379. doi: 10.1016/j.gaitpost.2015.07.005.

59. Diamond LE, Allison K, Dobson F, Hall M. Hip joint moments during walking in people with hip osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2018; 26: 1415-1424. doi: 10.1016/j.joca.2018.03.011.

60. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008; 16: 415-422. doi: 10.1016/j.joca.2007.12.017.

61. Kumar D, Manal KT, Rudolph KS. Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. Osteoarthritis Cartilage 2013; 21: 298-305. doi: 10.1016/j.joca.2012.11.008.

62. Werner FW, Ayers DC, Maletsky LP, Rullkoetter PJ. The effect of valgus/varus malalignment on load distribution in total knee replacements. J Biomech 2005; 38: 349-355. doi: 10.1016/j.jbiomech.2004.02.024.

63. Richards RE, Andersen MS, Harlaar J, van den Noort JC. Relationship between knee joint contact forces and external knee joint moments in patients with medial knee osteoarthritis: effects of gait modifications. Osteoarthritis Cartilage 2018; 26: 1203-1214. doi: 10.1016/j.joca.2018.04.011.

64. Kutzner I, Trepczynski A, Heller MO, Bergmann G. Knee adduction moment and medial contact force – facts about their correlation during gait. Plos One 2013; 8: e81036. doi: 10.1371/journal.pone.0081036.

65. Manal K, Buchanan TS. An Electromyogram-Driven Musculoskeletal model of the knee to predict in vivo joint contact forces during normal and novel gait patterns. J Biomech Eng 2013; 135. doi: 10.1115/1.4023457.

66. Diamond LE, Hoang HX, Barrett RS, Loureiro A, Constantinou M, Lloyd DG, et al. Individuals with mild-to-moderate hip osteoarthritis walk with lower hip joint contact forces despite higher levels of muscle co-contraction compared to healthy individuals. Osteoarthritis Cartilage 2020; 28: 924-931. doi: 10.1016/j.joca.2020.04.008.

67. Günther KP, Stürmer T, Sauerland S, Zeissig I, Sun Y, Kessler S, et al. Prevalence of generalised osteoarthritis in patients with advanced hip and knee osteoarthritis: The Ulm Osteoarthritis Study. Ann Rheum Diseases 1998; 57: 717-723. doi: 10.1136/ard.57.12.717.

68. Roaas A, Andersson GB. Normal range of motion of the hip, knee and ankle joints in male subjects, 30-40 years of age. Acta Orthop Scand 1982; 53: 205-208. doi: 10.3109/17453678208992202.

69. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514. doi: 10.1002/art.1780340502.

70. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29: 1039-1049. doi: 10.1002/art.1780290816.

71. Knoop J, van der Leeden M, van der Esch M, Thorstensson CA, Gerritsen M, Voorneman RE, et al. Association of lower muscle strength with self-reported knee

instability in osteoarthritis of the knee: results from the Amsterdam Osteoarthritis cohort. Arthritis Care Res (Hoboken) 2012; 64: 38-45. doi: 10.1002/acr.20597.

72. Nguyen US, Felson DT, Niu J, White DK, Segal NA, Lewis CE, et al. The impact of knee instability with and without buckling on balance confidence, fear of falling and physical function: the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage 2014; 22: 527-534. doi: 10.1016/j.joca.2014.01.008.

73. Fuss FK, Bacher A. New aspects of the morphology and function of the human hip joint ligaments. Am J Anat 1991; 192: 1-13. doi: 10.1002/aja.1001920102.

74. Snoeker B, Turkiewicz A, Magnusson K, Frobell R, Yu D, Peat G, et al. Risk of knee osteoarthritis after different types of knee injuries in young adults: a population-based cohort study. Br J Sports Med 2020; 54: 725-730. doi: 10.1136/bjsports-2019-100959.

75. Sommerfeldt M, Raheem A, Whittaker J, Hui C, Otto D. Recurrent Instability Episodes and Meniscal or Cartilage Damage After Anterior Cruciate Ligament Injury: A Systematic Review. Orthop J Sports Med 2018; 6: 2325967118786507. doi: 10.1177/2325967118786507.

76. Gooberman-Hill R, French M, Dieppe P, Hawker G. Expressing pain and fatigue: a new method of analysis to explore differences in osteoarthritis experience. Arthritis Rheum 2009; 61: 353-360. doi: 10.1002/art.24273.

77. Perrot S, Poiraudeau S, Kabir M, Bertin P, Sichere P, Serrie A, et al. Active or passive pain coping strategies in hip and knee osteoarthritis? results of a national survey of 4,719 patients in a primary care setting. Arthritis Care Research 2008; 59: 1555-1562. doi: 10.1002/art.24205.

78. Steultjens MP, Dekker J, Bijlsma JW. Coping, pain, and disability in osteoarthritis: a longitudinal study. J Rheumatol 2001; 28: 1068-1072.

79. Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: from mechanisms to treatment. Physiol Rev 2021; 101: 259-301. doi: 10.1152/physrev.00045.2019.

80. Zolio L, Lim KY, McKenzie JE, Yan MK, Estee M, Hussain SM, et al. Systematic review and meta-analysis of the prevalence of neuropathic-like pain and/or pain sensitization in people with knee and hip osteoarthritis. Osteoarthritis Cartilage 2021. doi: 10.1016/j.joca.2021.03.021.

81. Power JD, Perruccio AV, Gandhi R, Veillette C, Davey JR, Syed K, et al. Neuropathic pain in end-stage hip and knee osteoarthritis: differential associations with patient-reported pain at rest and pain on activity. Osteoarthritis Cartilage 2018; 26: 363-369. doi: 10.1016/j.joca.2018.01.002.

82. Blikman T, Rienstra W, van Raay JJAM, Dijkstra B, Bulstra SK, Stevens M, et al. Neuropathic-like symptoms and the association with joint-specific function and quality of life in patients with hip and knee osteoarthritis. PLoS One 2018; 13: e0199165-e0199165. doi: 10.1371/journal.pone.0199165.

83. Alshuft HM, Condon LA, Dineen RA, Auer DP. Cerebral cortical thickness in chronic pain due to knee osteoarthritis: the effect of pain duration and pain sensitization. PLoS One 2016; 11: e0161687. doi: 10.1371/journal.pone.0161687.

84. Barroso J, Vigotsky AD, Branco P, Reis AM, Schnitzer TJ, Galhardo V, et al. Brain gray matter abnormalities in osteoarthritis pain: a cross-sectional evaluation. Pain 2020; 161: 2167-2178. doi: 10.1097/j.pain.0000000000001904.

85. Cottam WJ, Iwabuchi SJ, Drabek MM, Reckziegel D, Auer DP. Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis. Pain 2018; 159: 929-938. doi: 10.1097/j.pain.0000000000001209.

86. Barroso J, Wakaizumi K, Reis AM, Baliki M, Schnitzer TJ, Galhardo V, et al. Reorganization of functional brain network architecture in chronic osteoarthritis pain. Hum Brain Mapp 2021; 42: 1206-1222. doi: 10.1002/hbm.25287.

87. Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, et al. Gray matter alterations in chronic pain: A network-oriented meta-analytic approach. Neuroimage Clin 2014; 4: 676-686. doi: 10.1016/j.nicl.2014.04.007.

88. Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ. Functional MRI of pain- and attention-related activations in the human cingulate cortex. J Neurophysiol 1997; 77: 3370-3380. doi: 10.1152/jn.1997.77.6.3370.

89. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000; 288: 1769-1772. doi: 10.1126/science.288.5472.1769.

90. McAlindon TE, Driban JB, Henrotin Y, Hunter DJ, Jiang GL, Skou ST, et al. OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthritis Cartilage 2015; 23: 747-760. doi: 10.1016/j.joca.2015.03.005.

91. Bennell KL, Bayram C, Harrison C, Brand C, Buchbinder R, Haas R, et al. Trends in management of hip and knee osteoarthritis in general practice in Australia over an 11-year window: a nationwide cross-sectional survey. The Lancet Regional Health – Western Pacific 2021; 12. doi: 10.1016/j.lanwpc.2021.100187.

92. Hinman RS, Nicolson PJ, Dobson FL, Bennell KL. Use of nondrug, nonoperative interventions by community-dwelling people with hip and knee osteoarthritis. Arthritis Care Res (Hoboken) 2015; 67: 305-309. doi: 10.1002/acr.22395.

93. Linsell L, Dawson J, Zondervan K, Rose P, Carr A, Randall T, et al. Population survey comparing older adults with hip versus knee pain in primary care. Br J Gen Pract 2005; 55: 192-198.

94. Hoogeboom TJ, Snijders GF, Cats HA, de Bie RA, Bierma-Zeinstra SMA, van den Hoogen FHJ, et al. Prevalence and predictors of health care use in patients with early hip or knee osteoarthritis: two-year follow-up data from the CHECK cohort. Osteoarthritis Cartilage 2012; 20: 525-531. doi: 10.1016/j.joca.2012.03.003.

95. Smink AJ, Dekker J, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, et al. Health care use of patients with osteoarthritis of the hip or knee after implementation of a stepped-care strategy: an observational study. Arthritis Care Res (Hoboken) 2014; 66: 817-827. doi: 10.1002/acr.22222.

96. Sakellariou G, Conaghan PG, Zhang W, Bijlsma JWJ, Boyesen P, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017; 76: 1484-1494. doi: 10.1136/annrheumdis-2016-210815.

97. The Royal Australian College of General Practitioners. Guideline for the management of knee and hip osteoarthritis. 2nd edn. East Melbourne VR, 2018.

98. Grimaldi A, Mellor R, Hodges P, Bennell K, Wajswelner H, Vicenzino B. Gluteal tendinopathy: a review of mechanisms, assessment and management. Sports Med 2015; 45: 1107-1119. doi: 10.1007/s40279-015-0336-5.

99. Griffin DR, Dickenson EJ, O'Donnell J, Agricola R, Awan T, Beck M, et al. The Warwick Agreement on femoroacetabular impingement syndrome (FAI syndrome): an international consensus statement. Br J Sports Med 2016; 50: 1169-1176. doi: 10.1136/bjsports-2016-096743.

100. Byrd JWT. Evaluation of the hip: history and physical examination. North American journal of sports physical therapy : N Am J Sports Phys Ther 2007; 2: 231-240.

Table 1. Prognostic factors for symptomatic and radiographic progression in hip and knee OA

Prognostic factors for symptomatic progression	Hip OA	Knee OA	Prognostic factors for radiographic progression	Hip OA	Knee OA
Age	-	'Strong evidence'	Heberden nodes	-	OR 2.66 [95% CI 1.46-8.84]
Ethinicity	-	'Strong evidence'	Baseline pain	-	OR 2.38 [95 CI 1.74-3.27]
Body mass index	-	'Strong evidence'	Varus malignment	-	'Strong evidence'
Infrapatellar synovitis	-	'Strong evidence'	High levels of hyalouronic acid		'Strong evidence'
Joint effusion	-	OR 1.35 [95% 0.99 to 1.83]	High levels of TNF-alpha	-	'Strong evidence'
Baseline severity	-	'Strong evidence'			
Presence of co-morbidity	'Strong evidence'	'Strong evidence'			
Large acetabular BML	OR 5.2 [95% CI 1.2 to 22.9]	-			
Large femoral head BML	OR 4.4 [95% 1.4 to 19.7]	-			
Chronic widespread pain	OR 5.0 [95% CI 2.9 to 9.1]	OR 3.2 [95% 1.9 to 5.3]			
Depression	OR 1.9 [95% CI 1.2 to 2.9]	-			
WORMS lateral cyst of score 1		OR 4.3 [95% CI 1.2 to 15.4]			
Increase of >2 in WORMS BML		OR 3.2 [95% CI 1.5 to 6.8]			

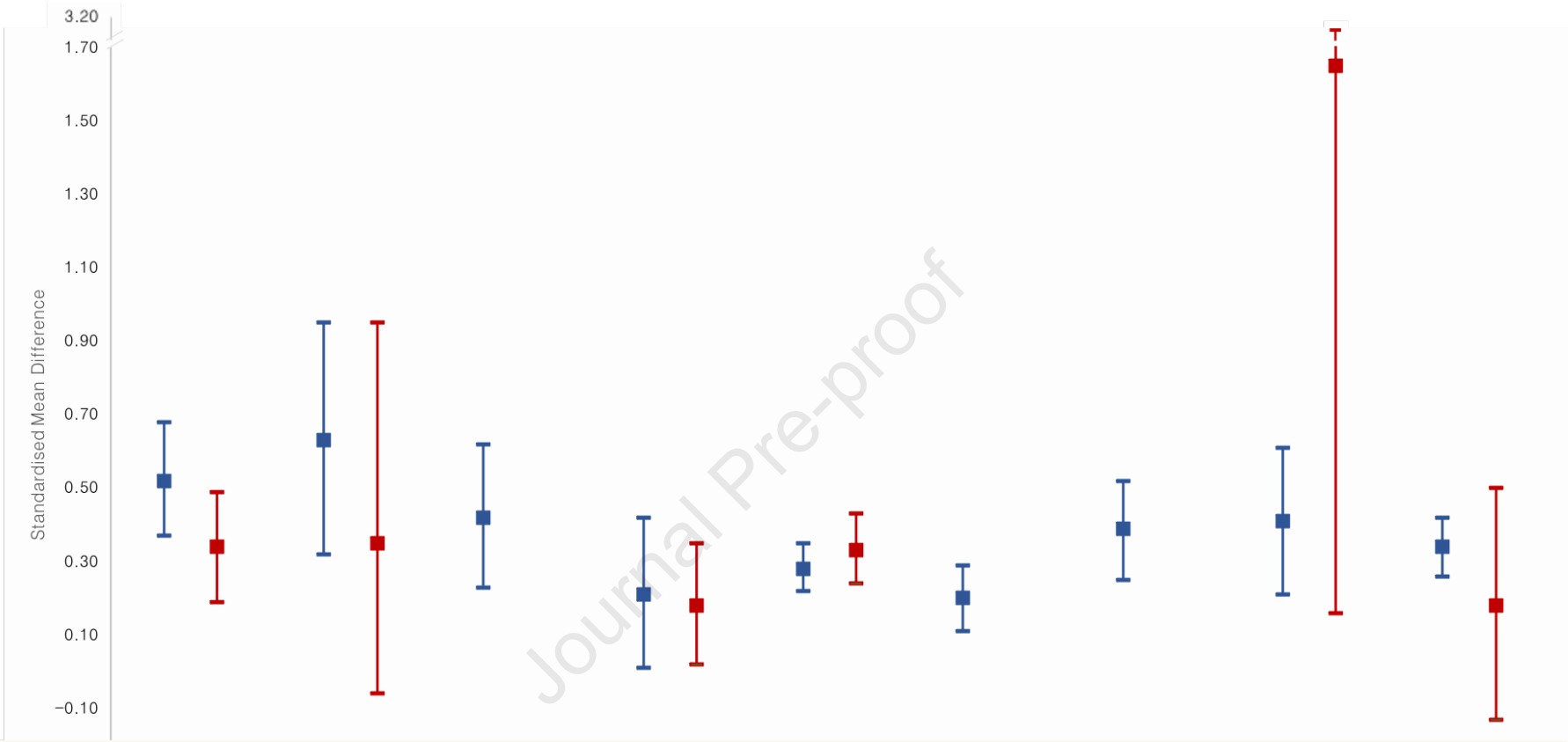
BML; bone marrow lesion; CWP: OR; Odds ratio; TNF tumor necrosis factor; WORMS whole-organ magnetic resonance imaging score; `-` no evidence reported

Table 2 Summary of highlighted differences between hip and knee OA

Prevalence	Lower in hip OA compared to knee OA. Hip OA rates similar in men and women, knee OA more prevalent in women.
Prognosis	Hip joint replacements are performed earlier than knee joint replacement, in people who are more likely to be male, younger and have a lower body max index than those undergoing knee replacement. Comorbidity, subchondral sclerosis, baseline pain severity and physical dysfunction are risk factors for hip OA progression. Several risk factors exist for knee OA progression.
Epigenetics	HOX-genes differ between hip and knee articular cartilage. miRNA (hip miRNA miR-451) differentially expressed between hip and knee OA articular cartilage.
Pathophysiology	Role of collagen IV potentially plays different role in hip and knee OA. Inflammatory process may differ in the serum and synovium between hip and knee OA. Higher serum COMP potentially correlates with hip OA symptoms, but not knee OA symptoms.
Anatomical and biomechanics	Different anatomical structures, hip joint is ball and socket, and knee joint is a complex hinge joint. Uncertain whether hip joint load predicts disease progression, whereas increasing evidence implicates higher knee joint load in structural disease progression. Relative to healthy controls, measures of joint load during walking are lower in hip OA, but higher in knee OA.
Clinical presentation	Restricted range of motion is more prominent in hip OA compared to knee OA. Joint instability is not often reported with hip OA but is commonly reported in knee OA.
Pain	Patient description of hip OA pain is more intense than of knee OA pain. Potentially less passive pain coping strategies (e.g. worrying, resting, retreating) in hip OA compared to knee OA. Probable neuropathic-like pain appears less prevalent in hip OA compared to knee OA and may depend on sex. Neuropathic-like symptoms potentially associates with pain-related quality of life in hip OA, but associates with physical dysfunction in knee OA.
Recommendations	Weight loss consistently recommended for management of knee OA where appropriate, but inconsistently recommend for management of hip OA due to lack of clinical trials in hip OA.

	Topical NSAIDs are strongly recommended for knee OA but with no evidence from clinical trials in hip OA, clinical practice guidelines do not make a recommendation for or against the use of topical NSAIDs for hip OA.
	Duloxetine is recommended for knee OA but recommendations for use in hip OA are inconsistent without any evidence from clinical trials in hip OA.
	Recommendations for use of hyaluronic acid injection for knee OA are inconsistent across clinical guidelines, but recommendations against the use of hyaluronic acid injection are consistent for hip OA.
Clinical practice	Exercise prescribed as a treatment more often for knee OA than hip OA
	Analgesics used more for hip OA than knee OA, but no difference in analgesics use between early hip and knee OA.
	Joint injections more frequently administered for knee OA than hip OA.
	Referrals for diagnostic radiology, is more frequent for hip OA compared to knee OA.

OA osteoarthritis; COMP: cartilage oligomeric matrix protein
HOX: Homebox genes; RNA ribonucleic acid



	Structured exercise		Mind–body program		Dietary weight management		Cognitive behavioral therapy		Oral NSAIDs		Topical NSAIDs		Duloxetine		Intra–articular corticosteroid		Intra–articular hyaluronic acid	
Joint	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip
No. of trials	23	8	6	1	2	No trials	4	4	9	3	7	No trials	4	No trials	22	3	52	3
No. of participants	2212	782	328	97	408	–	366	616	4513	1953	3575	–	1199	–	1529	200	7265	190