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Title: Osteoarthritis year in review 2021: epidemiology & therapy

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Running Title:

Year in review 2021: epidemiology & therapy

Abstract

This "Year in review" presents a selection of research themes and individual studies from the clinical osteoarthritis (OA) field (epidemiology and therapy) and includes noteworthy descriptive, analytical-observational, and intervention studies. The electronic database search for the review was conducted in Medline, Embase and medRxiv (15th April 2020 to 1st April 2021). Following study screening, the following OA-related themes emerged: COVID-19; disease burden; occupational risk; prediction models; cartilage loss and pain; stem cell treatments; novel pharmacotherapy trials; therapy for less well researched OA phenotypes; benefits and challenges of Individual Participant Data (IPD) meta-analyses; patient choice-balancing benefits and harms; OA and comorbidity; and inequalities in OA. Headline study findings included: a longitudinal cohort study demonstrating no evidence for a harmful effect of non-steroidal anti-inflammatory drugs (NSAIDs) in terms of COVID-19 related deaths; a Global Burden of Disease study reporting a 102% increase in crude incidence rate of OA in 2017 compared to 1990; a longitudinal study reporting cartilage thickness loss was associated with only a very small degree of worsening in pain over 2 years; an exploratory analysis of a non-OA randomised controlled trial (RCT) finding reduced risk of total joint replacement with an Interleukin-1 β inhibitor (canakinumab); a significant relationship between cumulative disadvantage and clinical outcomes of pain and depression mediated by perceived discrimination in a secondary analysis from a RCT; worsening socioeconomic circumstances were associated with future arthritis diagnosis in an innovative natural experiment (with implications for unique research possibilities arising from the COVID-19 pandemic context).

Key words

Clinical; epidemiology; osteoarthritis; treatment; review; COVID-19

Introduction and the context of the COVID-19 pandemic

The last year has been extraordinary. The COVID-19 infectious disease pandemic continued to grow worldwide with major direct and indirect health consequences (1). At the time of writing, there have been over 191 million cases confirmed globally (1). A socioecological framework of multiple interacting levels of influence can help us consider the complex and interacting ways in which the person with OA may have been impacted by the pandemic. We considered a similar broad framework in selecting the 12 diverse epidemiology and therapy themes included in this review.

The pandemic context also provides a unique natural experiment for epidemiologists to learn more about the impact of change in socio-ecological factors on OA outcomes. The final paper included in this review by Ikeda and colleagues (2) following the great east Japan earthquake and tsunami highlights one such novel example of learning emerging from great adversity.

Methods

A narrative review was conducted, beginning with a systematic search of Medline, EMBASE and medRxiv databases between 15th April 2020 to 1st April 2021, and limited to articles published in English (see Supplementary Material 1 for the Medline search filter). Observational studies, systematic reviews and phase III or IV trials, that were more likely to imminently influence clinical practice, were included. Table 1 summarises the eligibility criteria that were used to aid study selection. After removal of duplicates, 4,461 studies remained. Titles and abstracts were screened and prioritised by JQ with GP providing an additional opinion on a subset of articles resulting in 103 articles for full text screening. From the prioritised full texts salient emerging themes from the year were discussed iteratively between JQ, GP and PC and final study prioritisation and selection was

made. Final study inclusion was based on perceived study clinical importance, originality, quality, potential for controversy and personal interest. The 12 themes developed were presented at the OARSI 2021 World Congress, represented in an infographic (Figure 1) and shared on social media.

Table 1

Figure 1

Theme 1: COVID-19

It is still too soon to fully understand the impact of COVID 19 on people with OA with only 19 studies identified from our search including "Covid-19" or "coronavirus" in their titles or abstracts (with many of these being editorials and opinion pieces). Figure 2 offers a socioecological framework for how the Covid-19 pandemic may impact the individual through determinants of OA clinical outcomes.

Figure 2

Individual factors may have included changes in wellbeing (3), general health and health behaviours (such as physical activity, dietary intake and healthcare consulting behaviour) in turn impacting physical impairment, function and pain (4). In many countries, public policy and organisational changes aimed at infection control have reduced access to OA healthcare services and green spaces important for wellbeing and physical activity (5,6). Social distancing contributes to reduced social participation and isolation whilst changes in socioeconomic and employment circumstances may further impact wellbeing for many.

For those delivering OA clinical care, challenges included disruption in the delivery of face-to-face services (such as elective orthopaedics) (5) and rapidly adapting to new ways of remote working (for example telehealth, virtual consultations and online OA management programmes) (7-9). In 2020, during the early months of the COVID-19 pandemic, there was also international debate as to whether widely used NSAIDs complicate lower respiratory tract infections and may worsen prognosis of people infected with COVID 19 (10). Wong explored 2 large prospective UK cohorts between March and June 2020 using electronic medical record data from primary care linked to Office for National Statistics Covid mortality data. Cohort one was all people with a prescription for one or more NSAIDs in the previous 3 years (n=2,463,707), whilst Cohort 2 was all people with a diagnosis of RA or OA prior to study start (1,708,781). Current NSAID use (the exposure of interest) was defined as those prescribed NSAIDs in the 4 months prior to study start. Using adjusted cox-regression analysis they found no evidence of a harmful effect of routinely prescribed NSAIDs on COVID-19 related deaths in either Cohort 1- Hazard ratio 0.96 (95%CI 0.80, 1.14) or Cohort 2- HR 0.78 (0.64, 0.94). The authors concluded that treatment decisions about the routine use of NSAIDs need not be influenced by concerns of an effect on COVID-19 outcomes.

Theme 2: OA disease burden

Measuring OA disease burden is fundamental to understanding the size of the OA challenge. It has important implications for research funders and academics in prioritising their focus and is essential for health care providers in commissioning services which are matched to population needs. To investigate global incidence trends for musculoskeletal conditions, from 1990 to 2017, Jin and colleagues (11) used Global Burden of Disease (GBD) data and found that OA (in contrast to low back

pain and neck pain) had an annual global increase of 0.32% (95%CI 0.28, 0.36) in age standardised incidence rate (ASIR) or approximately 9% increase over the 28-year period. It is important to note that, without standardising for age, the ageing global population is actually driving a much greater increase in absolute numbers of new cases of OA (they quote a 102% increase in crude incidence rate between 1990 and 2017). This latter figure is highly relevant to the growing OA burden on health services and societies worldwide. Wu et al's (12) analysis of GBD data confirms this pattern in China but adds little to the previous analysis by Long et al (13) noted in the previous Year in Review (14). Whilst comparative analyses of trends in incidence of OA between countries and regions is important, measuring incidence is notoriously difficult and there is still a dearth of estimates from comparable data sources in low- and middle-income countries on which to confidently base inferences.

Whilst previous work has reported the increased health care burden of OA in cross-sectional studies, Kiadaliri and Englund (15) prospectively followed up patients with a new knee OA diagnosis to investigate temporal outcome trajectories. They conducted a matched longitudinal register-based study in Sweden (n=16,888). Linking multiple Swedish healthcare, occupational and social insurance registers they used early survival-adjusted methods to estimate 5-year incremental effects of knee OA per patient. Compared to age-sex, municipality-matched non-OA controls, patients with knee OA had, on average, substantially more healthcare consultations, medication use and net disability days.

Theme 3: Occupational risk in OA

A number of notable studies contributed knowledge on the association between occupation and OA (16-20). Wang et al's (16) systematic review (80 studies, 17 million participants) found 9 specific occupations associated with knee OA - farmer, builder, metal worker, floor layer, carpenter, miner, houseworker, service worker and craftsman. Higher exposures to occupational lifting, kneeling, climbing, squatting, and standing were potential mechanisms.

In addition to synthesising published estimates, pooling individual-level data from multiple comparable studies could enable more precise and detailed investigation of associations, including sex-specific analyses. Parsons and colleagues (19) demonstrated how participant-level data on predominant lifetime occupation from five US, UK and Australian cohorts may be harmonised into four categories (sedentary, light, light manual, heavy manual). Applying these categories to longitudinal data from the Chingford, Osteoarthritis Initiative and Multicentre Osteoarthritis cohorts, Perry et al (20) then reported stronger (albeit inconsistent across cohorts) associations between heavy manual occupations and risk of future radiographic knee OA in men than in women. A novel study investigating occupational and footwear associations with radiographic first metatarsophalangeal joint OA found no significant associations however, small sample size (n=209) and wide confidence intervals suggest low precision and the need for larger studies (21).

Theme 4: Joint morphology and OA prediction models

Morphology is important to the risk of OA, perhaps no more so than at the hip. van Buuren et al's (22) systematic review of 9 longitudinal studies (6,483 hips) found that shapes linked to acetabular dysplasia, cam-type deformity and acetabular retroversion/ excess anteversion most consistently emerged as independently associated with incident or progressive hip OA whilst other features only

increased the risk of hip OA when combined. We recommend the OARSI Imaging Year in Review by Oei for studies predicting OA outcomes from machine learning technologies applied to x-rays and MRI.

The large retrospective study (n=383,117) by Black and colleagues (23) was novel in predicting risk of new OA diagnosis at 5 years at *any* joint using routine Canadian primary care electronic health record data. The resulting prediction model (estimated area under the receiver operating characteristic=0.84), relied on just 5 predictors: age, sex, BMI, previous leg injury, osteoporosis. External validation could be a useful next step. We can expect increased machine learning applications to OA clinical, imaging and other biomarkers using big datasets like these.

Theme 5: Cartilage loss and pain

The development of OA pharmacotherapies focussed on chondroprotection has considered that such structure modification will result in improvement in clinical symptoms. A longitudinal study (n=600), nested within the OAI, by Bacon et al (24) investigated the relationship between cartilage loss and worsening knee pain after adjusting for bone marrow lesions (BMLs) and synovitis, before investigating whether the relationship between cartilage loss and pain was mediated by worsening synovitis or change in BMLs. They found that cartilage thickness loss was significantly associated with a small degree of worsening in pain over 24 months. A loss of 0.1mm of cartilage thickness over 2 years was associated with a small 0.32 increase in WOMAC pain (scale 0-20). This association was mediated by synovitis change (proportion mediated 14.1%) but not by change in bone marrow lesions (proportion mediated 2.8%).

The authors of this study consequently questioned whether pain in OA is triggered primarily by cartilage loss and suggested that demonstrating chondroprotection reduces knee pain may not be achievable.

Theme 6: Stem cell treatments

There is great interest in the OA field in cell-based treatments that may influence cartilage repair, such as stem cell therapy (25,26). However, the findings and reservations of Bacon et al (24) above, is a conflicting narrative to the hypothesis that such cartilage repair may lead to important clinical improvements in pain. The lack of adequately powered stem cell RCTs is a further problem in reaching robust conclusions regarding the clinical effectiveness of stem cell therapy. In our search from the last year, we found 6 new reviews but only 3 new small RCTs (n=40, 47 and 60) comparing an injected stem cell therapy intervention against active control intervention (27-29). Two of these studies (28,29), in patients with knee and temporomandibular joint OA, estimated between-group differences in pain at 6 months or beyond. In both instances these differences were not statistically significant.

Kim et al (26) systematically reviewed intra-articular injection of expanded Mesenchymal Stem Cells (MSC) for knee OA and investigated clinical outcomes of pain, function and OA structure. This review was selected because it specifically excluded studies which investigated MSC interventions with concomitant surgical procedures (which they highlighted as a common cause of uncertainty in the MSC efficacy literature). Kim et al identified 6 small trials of which 4 were quantitatively synthesised. Their largest meta-analysis included 125 participants again highlighting precision concerns and potential for small study bias, compounded by only 2 studies judged to be at low risk of bias.

Investigating multiple clinical outcomes, they found only VAS pain (0-100) at 6-12 months to be statistically significant between groups (mean difference -13.55, 95%CI [-22.19, -4.90] and concluded that *"the clinical evidence for the use of mesenchymal stem cells for knee OA remains limited"*.

Theme 7: Novel pharmacotherapy trials

This year a number of randomised placebo-controlled trials continued the search for novel OA pharmacotherapies, with interesting insights from a non-OA trial (30). Interleukin -1p is a critical cytokine involved in the OA process, however, whether its inhibition has clinical efficacy in OA is uncertain given previous largely negative clinical trials. Schieker and colleagues (30) carried out an exploratory analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) where 10,061 post-myocardial infarction patients (with elevated high-sensitivity C-reactive protein level, 2mg/L or greater) were randomised to either 50, 150, 300mg of Canakinumab or placebo subcutaneously every 3 months. They investigated time to first total knee or hip replacement (TKR/THR). Median follow up time was 3.7 years. Incidence rates for joint replacement were lower in the pooled Canakinumab groups compared to placebo: 0.31 and 0.54 events per 100-person years respectively. Similar findings were observed in analyses restricted to participants with a baseline history of OA. These exploratory findings suggest IL-1p inhibition substantially reduces TKR/THR rates and may indicate an effect on symptoms (the reason patients seek joint replacement); however, it is important to note the sample was selected for cardiac disease and systemic inflammation, not OA per se (15.6% had a reported medical history of OA at baseline). So further work will be required to understand the importance of treating patients with similar phenotype.

Weight loss is recommended in OA guidelines for the management of knee OA for people who are overweight or obese, though weight loss is notoriously difficult (31,32). Pharmacotherapy is one potential tool that may support weight loss. *Liraglutide* (a Glucagon-like peptide 1 receptor agonist used in managing Type II diabetes) taken at a dose of 3mg per day was investigated in a RCT of 156 overweight participants with knee OA following a diet-induced weight loss programme (33). The Liraglutide group achieved additional weight loss compared to control (weight change group difference 3.9KG 95%ci -6.9, -1.0). However, they found no between group difference in their coprimary outcome of KOOS pain, potentially due to insufficient magnitude of weight loss and or prior weight loss.

Several notable null-finding randomised controlled trials were published this year. Interleukin 6 (IL-6) has been suggested to have an important role in OA structural damage. *Tocilizumab*, an antibody against IL-6 receptor, was investigated in 83 patients with symptomatic hand OA (34). However, two 8mg intravenous infusions of *tocilizumab* four weeks apart was no more effective than placebo for pain relief at 6 weeks; the authors made the case for future long-term follow up studies that might explore structural outcomes. Some studies looked at existing pharmacotherapy agents used in other rheumatological conditions. *Colchicine*, an anti-inflammatory agent used in gouty arthritis was investigated in 64 adults with symptomatic hand OA. 1mg colchicine daily for 12 weeks was not effective for reducing pain, swollen joint count or increasing grip strength (35). Intravenous *zoledronic acid*, a bisphosphonate used in bone diseases and previously shown to reduce cartilage deterioration in animals by inhibiting subchondral bone resorption was investigated in adults with symptomatic knee OA and subchondral BMLs on MRI (n=223). Yearly 5mg *zoledronic acid* in a 100ml saline solution was not effective in reducing cartilage volume loss over 24 months or reducing secondary outcomes of pain or BML size (36).

A novel, topical 3.06% diclofenac gel *AMZ001* developed for potential faster and longer lasting action, administered over 4 weeks, was not shown to be more effective than placebo when delivered twice daily, though a once daily dose did find nominal significance over placebo (37). Notable conclusions from authors of recent pharmacotherapy systematic reviews were: that *"opioids provide no clinically relevant pain relief or reduction in disability compared to placebo in chronic OA pain and have low tolerability"* (38), (22 RCTs n=8952); tanezumab a monoclonal antibody that inhibits nerve growth factor *"can effectively improve pain and function"* compared with placebo in people with hip and knee OA but *"high quality large studies investigating long-term safety are required before drawing conclusions"* (39), (10 Phase III RCTs n=7211).

Though not a pharmacotherapy intervention per se, a small but notable complementary and alternative therapy RCT by Wang and colleagues (40) investigated the effectiveness of *Curcuma longa* (CL) extract for the treatment of symptoms and effusion-synovitis in a randomised placebo- controlled trial of participants with knee OA and ultrasonography-defined effusion synovitis (n=70). They found CL improved VAS pain compared to placebo over 12 weeks (-9.1mm, 95%CI, -17.8to - 0.4mm) but not the co-primary outcome of effusion-synovitis volume (3.2 mL, 95%CI -0.3 to 6.8 mL). The incidence of adverse events was similar between groups. The authors called for larger multicentre trials to further assess the clinical significance.

Theme 8: Therapy for less well researched OA phenotypes

National and international guideline committee authors have repeatedly highlighted the need for more OA research on joints other than the knee and hip (31,32). Once more, this year the majority

of published research was on knee OA with a small number of RCTs investigating therapy for hand or foot OA.

Though education, strengthening exercise, splinting and topical NSAIDs are recommended for base of thumb OA, their individual effect sizes are small and it is not known if combined conservative therapies lead to greater benefits (41,42). Deveza and colleagues (42) conducted a RCT (n=204) to investigate the effectiveness of these treatments delivered in 2 face-to-face physiotherapist consultations combined compared to education alone. Co-primary outcomes, at 6 weeks, were pain (assessed by VAS 0-100mm) and hand function (Functional Index for Hand Osteoarthritis, 0-30; higher scores representing worse function). Hand function improved significantly more in the combined intervention arm (between-group difference, -1.7 units; 97.3%CI, -2.9 to -0.5; P = .002). Both groups showed similar improvements in pain (between-group difference, -4.2 mm; 97.3%CI, -11.3 to 3.0; P = .19) at 6 weeks with pain reduction significantly greater at 12 weeks in the combined therapy group (-8.6 mm; 95%CI, -15.2 to -2.0; P = .01).

Carbon fibre shoe-stiffening inserts, which reduce the rate and magnitude of big toe dorsiflexion, were superior to sham shoe inserts for reducing first metatarsophalangeal joint (MTP) OA pain in a RCT (n=90) by Munteanu et al (43). Carbon fibre shoe-stiffening inserts improved pain at week 12 (measured by the 0-100 Foot Health Status Questionnaire, adjusted mean difference 6.66, 95%CI 0.65, 12.67), however, minimum important difference in pain was not achieved and stiffening inserts were also linked to increased likelihood of foot pain (at joints other than the first MTP joint). The effect sizes in these trials were small.

Theme 9: Benefits and challenges of Individual Participant Data meta-analyses

Rather than extracting summary (aggregate) data from study publications, IPD studies involve seeking participant-level original research data directly from the researchers responsible for each study. These data can then be re-analysed centrally and combined, if appropriate, in meta-analyses (44,45). A few IPD meta-analyses using RCT data have been conducted in the OA field to date addressing important clinical effectiveness and subgroup questions (46-48). This year saw further IPD meta-analysis studies published including one using RCT data (49) and one using observational cohort data to investigate outcome risk over time (50). Persson and colleagues (49) predicted response to topical NSAID in OA using IPD meta-analysis of 15 RCTs. They found topical NSAIDs were superior to placebo (-6, 95%CI -9, -4 on a 0-100 scale), with women and individuals with higher baseline pain reporting greater pain relief after treatment, but; no differences in efficacy were observed for age, BMI, features of inflammation, duration of complaints or radiographic OA severity. Knee OA and time to all-cause mortality was investigated by Leyland et al (50) using meta-analysis of individual participant-level data from six international community-based cohorts. Painful OA (HR 1.35 95%CI 1.13, 1.63) and painful and radiographic OA (HR 1.37 95%CI 1.22, 1.54) were associated with reduced time to all-cause mortality (with radiographic OA alone showing no association). These two studies provide an excellent opportunity to revisit and reflect on IPD methods, potential advantages, disadvantages and practical realities across different study types (Table 2).

Table 2

In summary, whether these studies will provide a small step forward or a giant leap for the OA field is still emerging and the reality likely lies somewhere in between.

Theme 10: Patient choice, balancing benefits and harms

People with OA and the healthcare professionals who support them have to weigh the individual benefits and risks of a suite of interventions. Patient treatment choice is of great clinical importance in guiding research priorities and person-centred care. Table 3 compares 3 different discrete choice experiment studies (DCE) (51-53) highlighting alternate method options and key findings.

Understanding patient preferences through DCEs and combining these with cost-effectiveness data and healthcare practitioner expertise can help inform best practice and care commissioning. These findings can also help shape future intervention development research.

Table 3

Theme 11: OA and comorbidity

Investigating OA and comorbidity epidemiology can help elaborate interrelated causal mechanisms, complexities and considerations in person-centred condition management and can help us further understand the burden of OA. The positive association between OA and risk of Alzheimer's Disease (54) was restated in a large longitudinal study by Innes and Sambamoorthi (55) whilst Jacob and Kostev (56) found patients aged 18 and over with clinician diagnosed OA are more likely to suffer at least one future fracture over 10 years when matched for sex, age and key fracture risks hazard ratio 1.55, (95% CI 1.50-1.60).

Considering studies that identify comorbid groups at increased risk of negative health outcomes who require alternative or tailored care, King (53) found comorbid hypertension, gastrointestinal diseases, depressed mood and higher numbers of troublesome joint pain sites were all associated with higher opioid use in Canadian patients with knee OA consulting an orthopaedic surgeon, whilst McKeivitt and colleagues (57) found presence, number and specific types of comorbidity were associated with lower self-reported physical activity using baseline data from two large RCTs.

Theme 12: Inequalities in OA

This year emerging data from the COVID-19 pandemic, the Black Lives Matter and gender equality movements alongside the "coin model of privilege" theory have brought into keen focus societal and health inequalities (59,60). Here we highlight two studies investigating inequalities in OA that have moved beyond simple description to explore mechanisms of inequalities in OA health outcomes.

Investigating cumulative disadvantage and disparities in depression and pain, with a focus on the role of perceived discrimination, McClendon and colleagues (61) conducted secondary data analysis using baseline data from a US veteran RCT (n=517). They measured "cumulative disadvantage" as the number of socially disadvantaged groups to which each participant belonged (i.e. female gender, African American race, income<\$20,000, and/or unemployed due to disability). Using linear regression and Sobel's test of mediation, they found cumulative disadvantage was significantly associated with higher perceived discrimination, pain and depression. Perceived discrimination mediated 41% of the total effect of cumulative disadvantage on depression and 9% of the total effect on pain.

We started this review highlighting how the COVID-19 pandemic context could be utilised as a natural experiment to evaluate the effect of change in socioecological factors on OA outcomes. We finish with a similar innovative study that investigated the causal effect of deteriorating socioeconomic circumstances on new onset "arthritis" using a natural experiment in Iwanuma city from the 2011 great east Japan earthquake and tsunami (2). Ikeda sought to make causal inferences by applying a two-stage least squares instrumental variable method using "distance from the coastline" as the instrumental variable (Figure 4). The authors claimed a causal association between both subjective worsening economic circumstances and housing damage and the development of arthritis (0.08 (0.03 to 0.12) and 0.02 (0.01 to 0.04), respectively). Valid causal inference from such a study relies on fulfilling many assumptions relating to the nature and timing of the 'intervention' and outcomes and the choice of instrument, but intelligent use of the full range of methods available to us can improve our chances of adding new, important knowledge.

Figure 4

Conclusion

In conclusion, the breadth of themes and studies selected in this review highlight the complexity of OA epidemiology and therapy and showcase the variety and innovation of outstanding contributions to the field in this difficult year. We would like to finish by acknowledging the OARSI community, researchers, clinicians and participants for the many fine OA studies and please forgive us if your work was not included here.

Contributions

All authors were involved with the study design, study searching, and manuscript editing. All authors reviewed the final manuscript.

JQ was lead author for the work, manuscript drafting and is responsible for the content.

Competing interest statement

Jonathan Quicke has no financial conflict of interest and is an unfunded member of the NICE OA guideline committee. Philip Conaghan has done speakers bureaus or consultancies for AbbVie, Amgen, Astra Zeneca, Contura, Eli Lilly, Galapagos, Novartis, Pfizer and UCB. Nadia Corp and George Peat have no conflicts of interest to declare.

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Supplementary Material 1

MEDLINE (Ovid) Search strategy

The following table is an explanation of the symbols used in the search strategy below.

/	indicates an index term (MeSH heading)
exp	before an index term indicates that all subheadings were selected
.kf.	indicates a search for a term as a word in keyword

- 1 exp *Osteoarthritis/
- 2 osteoarthritis.kf.
- 3 limit 2 to ("in data review" or in process)
- 4 1 or 3
- 5 limit 4 to ed=20200415-20210331
- 6 limit 4 to dt=20200415-20210331
- 7 5 or 6
- 8 exp animals/ not humans/
- 9 7 not 8
- 10 limit 9 to english language

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Figure legends

Table legends

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Figure legends

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Table 2: Exploring varying methods and emerging benefits and challenges of IPD OA studies

Persson et al 2020	Leyland et al 2021
Study Title Predicting response to topical NSAID in OA: an individual patient data meta-analysis of randomized controlled trials	Knee OA and time-to all-cause mortality in six community-based cohorts: an international meta-analysis of individual participant-level data.
Summary methods <ul style="list-style-type: none">• 15 (of 63 eligible) RCTs (n=1951 on topical NSAIDs) including 11 placebo controlled RCTs• 1-stage individual patient data meta-analysis• Mixed effects multilevel model	<ul style="list-style-type: none">• 6 (of 7 identified) community-based longitudinal cohorts available for analysis• 2-stage IPD meta-analysis• Cox-proportional hazard models• Pooled Hazard ratios using the Hartung-Knapp modification for random-effects meta-analysis
Key benefits <ul style="list-style-type: none">• More data and power to investigate subgroups (interactions)• May increase knowledge of patient-level predictors of response	<ul style="list-style-type: none">• Standardised data harmonisation and analysis across multiple cohorts• Publication bias was reduced by not being limited to the inclusion of only previously published studies
Key challenges <ul style="list-style-type: none">• Data availability bias (e.g. of 63 eligible RCTs, 15 provided IPD & key variables of interest were not available to investigate such as central sensitisation, psychological factors and synovial inflammation)• Unable to conduct IPD for topical capsaicin as planned as no data custodians were willing or able to contribute data (n=10 eligible RCTs)	<ul style="list-style-type: none">• Data availability bias (e.g. only possible to investigate variables in the primary datasets hence key potential confounding variables like <i>physical activity</i> may be missing or inconsistently measured across datasets and certain potential mediators of interest like <i>medication use</i> could not be investigated).• Substantial time and resources required

to gather harmonise and analyse data

Table 3: Discrete choice experiments (DCE)

Hiligsmann et al 2020	Turk et al 2020	Arslan et al 2020
<p>Study concise aim</p> <p>To evaluate patient preferences for OA treatment</p>	<p>To quantify preferences for attributes of potential pharmaceutical analgesic treatments</p>	<p>To determine patients', healthcare providers' and insurance company employees' preferences for hip and knee OA care</p>
<p>Methods to inform DCE questionnaire</p> <ul style="list-style-type: none">• Scoping reviews; patient interviews; a patient survey, and; an expert meeting with one OA patient	<ul style="list-style-type: none">• Series of focus groups	<ul style="list-style-type: none">• Existing qualitative studies on patient preference for hip and knee OA care and OA expert interviews, attributes of care were compiled and ranked in terms of importance
<p>Discrete choice experiment methods</p> <ul style="list-style-type: none">• DCE survey (n=253 OA patients from 7 European countries)• Random parameters logit model was used to estimate patients' preferences and a latent class model was also conducted to explore preference classes	<ul style="list-style-type: none">• Online stated-preference survey (n=602 of whom 400 had OA) with both a DCE of pharmaceutical attributes (i.e. of non-opioid NGF inhibitors, NSAIDs and opioids) and best-worst scaling exercise (to quantify the relative importance of an additional set of treatment-related risks)• Random parameters logit model was used to estimate patients' preferences	<ul style="list-style-type: none">• DCE survey (n=648 patients, n=76 healthcare providers and n=150 insurance company employees)• Choice observations for each participant group were analysed separately using a logit model and an additional panel latent class model (to identify heterogenous patient patterns or "latent classes")
<p>Key findings</p> <ul style="list-style-type: none">• The most important outcomes of treatment were impact on disease progression and improvement in pain and walking	<ul style="list-style-type: none">• The most important attributes were improving symptom control followed by reducing risk of physical dependence• The most important risks to avoid (in descending order) were a 0.6% increased risk of a stroke, a 25% annual	<ul style="list-style-type: none">• All participants preferred a joint consultation by GP and orthopaedist with low out of pocket costs.• Substantial heterogeneity in patient preference with 4 latent classes of patients' preferences identified.

risk of becoming physically dependent on a prescription medicine, a 0.5% increased annual risk of a heart attack, a 4% increased annual risk of severe joint problems.

Key novelty

- Investigated patient preferences by country
- First study to evaluate preferences for features that differentiate analgesics including NGF inhibitors
- First DCE study to include multiple stakeholders and attributes of healthcare settings and human resources who provide care

Key: DCE=Discrete Choice Experiment; NGF= Nerve Growth Inhibitor; GP=General Practitioner

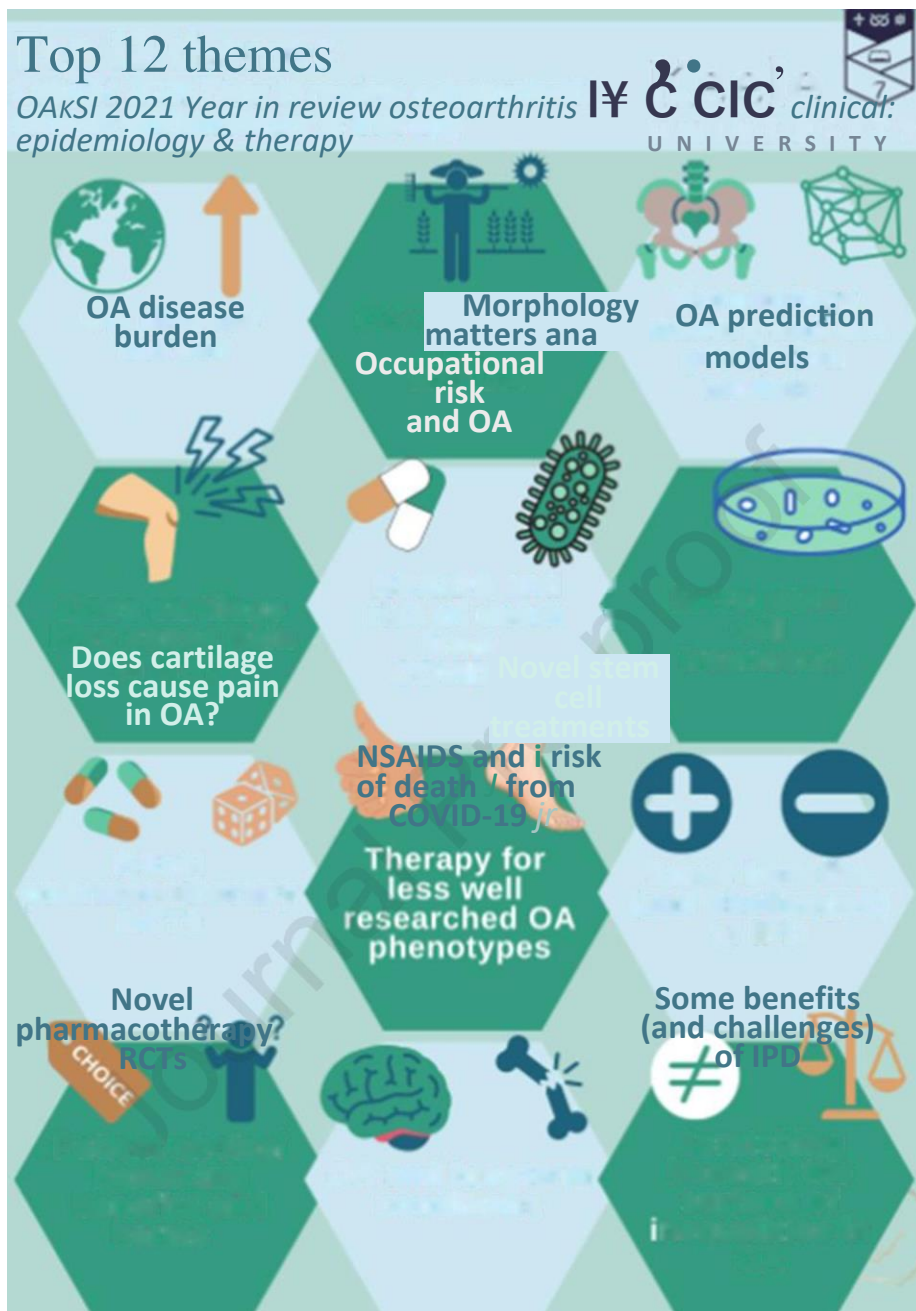
Table 1: Study eligibility criteria	Inclusion criteria	Exclusion criteria
Study Methods	<ul style="list-style-type: none"> • Randomised controlled trials (Phase III or IV) • Quasi-randomised controlled trial (where the method of allocation is known, but is not considered strictly random, e.g. alternation, medical record number). • Cohort studies • Systematic reviews 	<ul style="list-style-type: none"> • Narrative reviews • Case reports • Case series
Publications	<ul style="list-style-type: none"> • Full text, published studies in English • Studies from all countries 	
Participants	<ul style="list-style-type: none"> • Adults with Osteoarthritis i.e.: Adults with joint pain aged 45 years and over (mean age over 45 years)/ adults with OA diagnosed by x-ray OR according to clinical criteria or by a health care professional • Adults with self-reported OA • N.B: If population is mixed (e.g. OA and rheumatoid arthritis, include if 	<ul style="list-style-type: none"> • Adults with joint pain attributable to conditions other than OA • Rheumatoid arthritis/ other defined inflammatory rheumatological problems • Pre-operative or postoperative patients (people on waiting lists for knee/hip surgery or immediately following surgery) • Animal based studies • Ex vivo/ in vitro studies • Studies of children
Comparator for RCTs	<ul style="list-style-type: none"> • Placebo controlled studies 	
	<p>over 50% of participants have OA</p>	
Intervention/ exposure	<ul style="list-style-type: none"> • Any pharmacotherapy intervention • Any exposure 	<ul style="list-style-type: none"> • Surgical interventions • Interventions and exposures and interventions covered by other OARSI year in review. For example, exercise and rehabilitation interventions, biomechanics focussed studies OR epigenetic studies

- Pharmacotherapy studies with nonplacebo comparisons

Outcomes

- Clinical outcomes including pain and/or function and or measure of disease progression or surrogate measure of disease progression (for example, joint replacement surgery)

Figure 1: OARSI 2021 epidemiology & therapy top themes.



Patient choice/
balancing
benefits and
harms

OA and longterm
conditions

Scratching
beneath the
surface of
nequalities in
OA

Figure 2: Socioecological framework of OA during Covid 19 pandemic

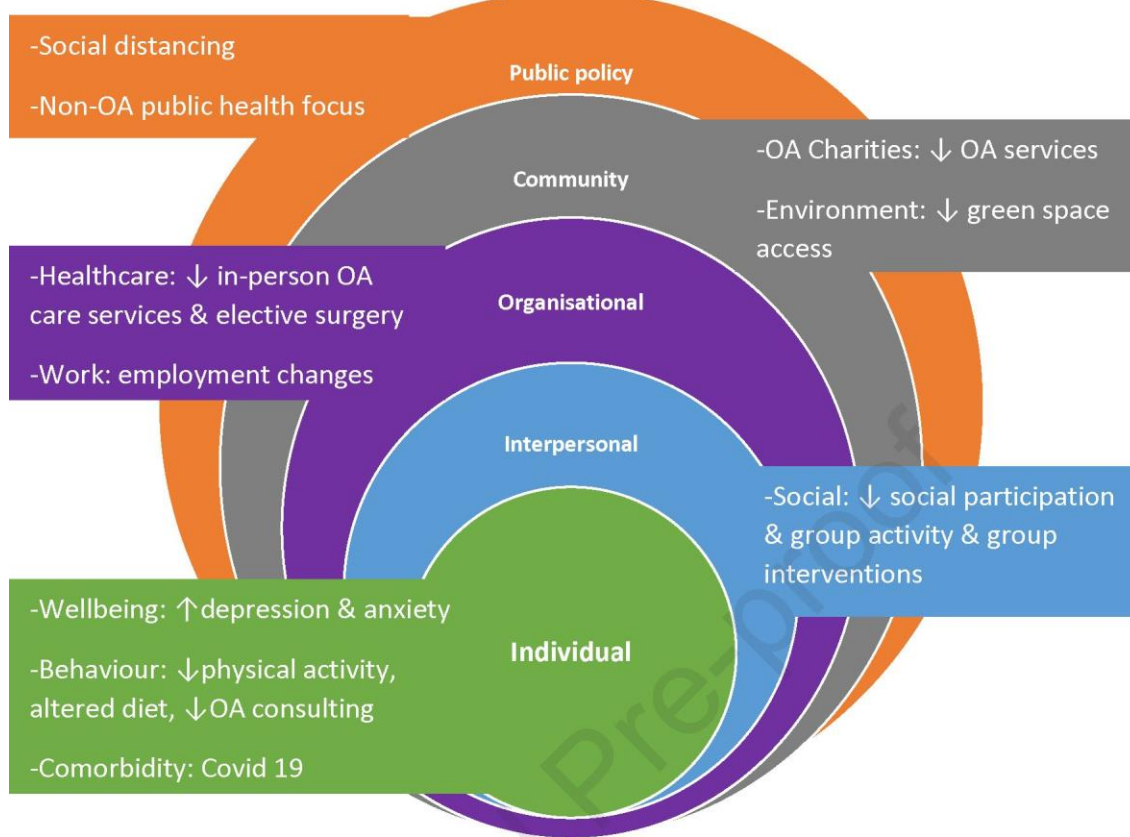
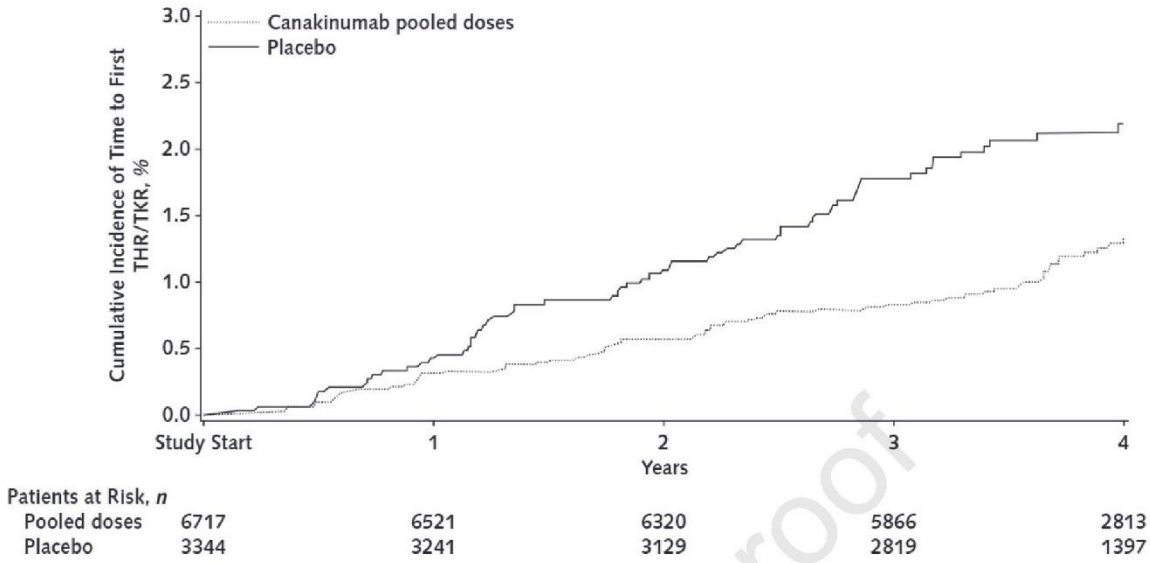


Figure 3: Cumulative incidence rates for THR/TKR in the full trial sample



Footnote: Cumulative incidence of THR/TKR in the placebo group compared with all participants who received canakinumab, regardless of dose. [Figure reproduced with author's permission (Schieker et al 2020, Annals of Internal Medicine)]

Figure 4: Directed Acyclic Graph of worsening socioeconomic circumstances and arthritis onset

