

Original article

Association between current medication use and progression of radiographic knee osteoarthritis: data from the osteoarthritis initiative

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Abstract

Objective. Use of specific medications may accelerate the progression of radiographic knee OA (RKOA). Our aim was to examine the effect of medication use on the progression of RKOA.

Methods. We used longitudinal data from the Osteoarthritis Initiative (OAI), an observational study of risk factors for knee OA. At baseline, we selected participants with RKOA (Kellgren–Lawrence grade ≥ 2) and excluded those with a history of knee-related injury/surgery and other musculoskeletal disorders. Current medication use (use/non-use in the previous 30 days) and radiographic medial minimum joint space width (mJSW) data were available at baseline and annually up to 96 months follow-up. We used random effects, panel regression to assess the association between current medication use (non-users as reference group) and change in mJSW.

Results. Of 2054 eligible participants, 2003 participants with baseline mJSW data were included [55.7% female, mean age 63.3 (s.d. 8.98) years]. Of seven medication classes, at baseline NSAIDs were the most frequently used analgesia (14.7%), anti-histamine (10.4%) use was frequent and the following comorbidity medications were used most frequently: statins (27.4%), anti-hypertensives (up to 15.0%), anti-depressant/anti-anxiety/psychotropics (14.0%), osteoporosis-related medication (10.9%) and diabetes-related medication (6.9%). Compared with current non-users, current use of NSAIDs was associated with a loss of mJSW ($b = -0.042$, 95% CI -0.08 , -0.0004). No other associations were observed.

Conclusions. In current users of NSAIDs, mJSW loss was increased compared with current non-users in participants with RKOA. Clinical trials are required to assess the potential disease-modifying effects of these medications.

Key words: medication, knee osteoarthritis, progression, analgesic

Rheumatology key messages

- In current users of NSAIDs, radiographic medial minimum joint space width was reduced.
- The association between current use of NSAIDs and radiographic medial minimum joint space width was not clinically significant.
- Clinical trials are needed to examine the disease-modifying effects of medications in radiographic knee OA.

Introduction

OA, a chronic disorder typically characterized by inflammation, cartilage loss and bone remodelling [1], is a

leading cause of global disability and reduced quality of life [2]. The knee joint is frequently involved, with up to one in three adults aged ≥ 45 years showing evidence of radiographic knee OA (RKOA) [3]. Due to a lack of effective disease-modifying treatments for knee OA, current medications aim to alleviate painful symptoms and

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improve function. The long-term effects of these medications on structural progression are, however, not yet known.

Structural progression of knee OA has been associated with gradual worsening of painful symptoms [4–6]. The current standard of care for OA, as recommended by many organizations [7–13], is to manage symptoms using non-pharmacologic and pharmacologic treatments. Most guidelines recommend the use of analgesics as first-line interventions after core treatment. NSAIDs, cyclooxygenase II (COX-2) inhibitors and IA therapies are among the most common analgesics used for symptom relief [14]. The effects of analgesia on structure in knee OA are unclear and the mechanisms for structural progression remain largely unknown.

Evidence from few *in vitro* studies suggests that some NSAIDs may inhibit cartilage matrix synthesis [15, 16], thereby contributing to OA development. However, other analgesia may inhibit COX, impairing the production of prostaglandins [17] and thus protecting against the development of inflammation, bone cysts and osteophytes [18]. Most data, but not all, suggest that the use of analgesia may be associated with the progression of RKOA [14, 19–24]. With specific reference to steroid-based interventions, a recent study showed that IA CS use over 4 years in RKOA patients was associated with an increased risk of structural progression compared with those having never received an IA CS injection [19]. Similar findings were observed in a randomized trial of IA triamcinolone vs saline that showed steroid use over 2 years was associated with significantly greater cartilage volume loss in symptomatic knee OA patients [20]. In contrast, there are data suggesting that CS use has no significant effect on structural progression in knee OA [25, 26]. Studies of longer duration are needed to provide clarity.

OA has been associated with an increased risk of comorbidity including diabetes, cardiovascular disease and hypertension [27, 28], with prevalent comorbidity occurring in up to 67% of OA patients [29]. Understanding the impacts of prescribed medications on disease progression of OA represents a considerable health concern. Several studies have shown that diabetes is associated with knee OA [30, 31], though recent evidence suggests that the use of diabetes medication may be protective [32–34]. The underlying mechanism remains unclear; however, metformin use might reduce inflammation by decreasing the number of Th17 cells and increasing the number of Treg cells [35]. Further exploration is needed to confirm these effects in long-term observational studies. In addition, hypertension has been shown to be associated with degenerative cartilage changes on MRI in knee OA [36], with the mechanism thought to be related to ischaemia, cartilage loss and bone remodelling [37]. Compared with non-use, hypertensive medication use has been shown to be associated with reduced odds of incident RKOA (odds ratio 0.4, 95% CI 0.1, 1.0) [38]. Further studies are required to explore the overall effects of medication and disease on the progression of RKOA.

Our aim was to conduct an exploratory analysis of RKOA progression among medication users and non-users to identify pharmacological interventions that may be associated with the disease pathway. This may, in turn, identify potential areas for disease-modifying treatment development.

Methods

Participants

We utilized data from the Osteoarthritis Initiative (OAI), a publicly available, multicentre, observational cohort study of risk factors for knee OA. Detailed study methods are available online (<http://oai.epi-ucsf.org>). In brief, 4796 men and women aged between 45 and 79 years were recruited at four clinical sites across the USA. Participants eligible for the current study were those with evidence of baseline RKOA [Kellgren–Lawrence [39] (KL) grade ≥ 2] in either/both knee(s). We excluded participants with evidence of inflammatory arthritis, including RA, gout or PsA, and a history of knee-related injury and/or surgery at baseline. Further, we only included participants with radiographic outcome data at baseline (see ‘Radiographic assessment’ section). Ethical approval was not required for any aspect of the work presented in this manuscript.

Radiographic assessment

Bilateral standing postero-anterior fixed-flexion knee radiographs were acquired annually at baseline, 12, 24, 36, 48, 72 and 96 months’ follow-up using a SynaFlexer™ frame (Synarc, San Francisco, CA, USA) [40, 41]. Minimum and fixed location, quantitative joint space width (JSW) measurements (mm) of the medial and lateral compartments were acquired using a semi-automated approach [42, 43]. In brief, the software delineates the femoral condyle and tibial plateau joint margins, with medial minimum JSW (mJSW) defined as the minimum distance between the two contours of the medial tibio-femoral compartment. Radiographs were scored for OA using the KL criteria, with KL ≥ 2 indicating the presence of RKOA [osteophyte(s) with joint space narrowing].

Exposure: current medication use

Data on current medication use was available at baseline and at follow-up (12, 18, 24, 30, 36, 48, 72 and 96 months’ follow-up) [41]. All currently used prescription medications (used in the previous 30 days) were captured according to the medication inventory method [41, 44], a process by which study participants were asked to bring all current medications to the study visit. In our study, a musculoskeletal research fellow (X.W.) categorized medication compounds into seven medication classes of interest, which were cross-checked by a pharmacist (C.A) with over 10 years of experience (see [Supplementary Table S1](#), available at *Rheumatology*

online). In participants with medication data, participants were classified as either ‘current users’, if they reported use of a given medication within the previous 30 days, or ‘current non-users’ if they had no reported use of prescription medication category at the corresponding visit. Participants with no medication data at each respective visit were treated as missing. Data were not available for medication dosage.

Given the evidence gaps, conflicts in current data and what is currently known of the disease pathway, we decided *a priori* to focus on musculoskeletal analgesia, osteoporosis-related medications, statins, anti-hypertensive medications, diabetes-related medications, anti-histamines and anti-depressant/anxiolytic/psychotropic medications.

Outcome measures

Progression of RKOA was assessed using a single endpoint, change in mJSW. Good reliability of mJSW measurement has been reported previously [43, 45].

Selection of index knee

We used a single knee from each participant: the most radiographically severe knee. In cases of bilateral RKOA (based on KL scoring), we selected the knee with the smallest mJSW at baseline and followed that knee across follow-up, unless the mJSW of the most severe knee was equal to 0 in which case we used the contralateral knee. Further, in cases of bilateral knee OA, if mJSW measures were available for a single knee only, we used the knee with data. If a participant had two eligible knees with equal mJSW, we used the most painful knee at baseline, consistent with previous methods [19]. In cases of bilateral knee OA, with equal mJSW and pain symptoms, we selected the right knee for analysis. We excluded participants with baseline unilateral RKOA that had mJSW equal to 0 (bone-on-bone) as they were unable to progress.

Assessment of covariates

Baseline covariates that were adjusted for included age, BMI, sex, race and OA severity (as mJSW). Additional covariates included baseline pain (for the corresponding knee) with pain assessed using the WOMAC questionnaire. The WOMAC pain subset was scored on a 0–5 rating scale for each component, with 0 = no pain and 20 = severe pain. Moreover, we adjusted for baseline knee alignment (for the corresponding knee), categorized as neutral, varus or valgus malalignment, and baseline Charlson comorbidity score [46] (range 0–12).

Statistical analysis

Descriptive statistics were tabulated with normally distributed variables presented as means and s.d., and non-normally distributed variables presented as medians and interquartile range. Categorical variables were presented as counts and percentages.

We used random effects multiple linear panel regression to explore the relationship between current medication use, for each of the respective medication groups, and change in mJSW; this approach was suited to handling repeated measures of varying sample size [47].

Data across all available visits were included in the analysis with the exception of baseline, to limit the effects of collinearity. In the model, mJSW (at all available visits except baseline) was coded as the outcome with current medication use (coded as 0 = current non-use, 1 = current use) and visit (coded as 1 = 12 months, 2 = 24 months, 3 = 36 months, 4 = 48 months, 5 = 72 months and 6 = 96 months) as the exposure variables. Visit was included as a categorical variable in the model, thereby allowing the effect between medication use and mJSW to be varied over time; this was to allow for natural variability in pattern of medication use, which has been shown to occur with the use of analgesia [48]. The exposure arm therefore, tests whether mJSW differed between current medication users and current non-users at each respective visit. The associations were reported as unstandardized *B* coefficients. The output of these models therefore shows the overall effect of the use of the target medication and the resulting change in mJSW, with current non-users as the reference group. All models were adjusted for potential confounders. To account for the correlation between repeated measures within individuals, we set the patient identifier as the panel variable.

As part of the OAI study, participants with evidence of end-stage radiographic disease at 48 months (i.e. KL = 4 or ‘very narrow JSW’) did not have their JSW measured in their corresponding knee(s) at the 72- and 96-month visits [41]; the proportion of missingness can be seen in [supplementary Table S2](#), available at *Rheumatology* online. To examine the effects of this, we also performed a sensitivity analysis by restricting the analysis to 48 months’ follow-up. All statistical analyses were completed using Stata/IC version 15.0 with a two-sided *P*-value of 0.05 considered statistically significant.

Results

Participants and descriptive data

Of the 2054 eligible participants, 2003 participants had data on mJSW at baseline and were included in our analysis ([supplementary Fig. S1](#), available at *Rheumatology* online). The mean age was 63.3 years (s.d. 8.98) and 55.7% were female. [Table 1](#) shows the demographic, clinical, radiographic and medication characteristics of the analysed study participants. At baseline, prescription NSAIDs were the most commonly used analgesics (14.7%), followed by COX-2 inhibitors (9.7%), CS (9.5%), opioid analgesics (5.1%) and paracetamol (3.8%). Further, use of a comorbidity-related medication was common.

In multivariate analysis, current use of NSAIDs was associated with the loss of mJSW compared with

TABLE 1 Characteristics of eligible study participants at baseline ($N = 2003$)

Characteristics	
Age (years)	63.3 (8.98)
Missing, n (%)	42 (2.1)
Sex	
Male, n (%)	888 (44.3)
Female, n (%)	1115 (55.7)
BMI (kg/m²)	29.8 (4.8)
Missing, n (%)	4 (0.2)
Race, n (%)	
White or Caucasian	1541 (76.9)
Black or African American	413 (20.6)
Asian	13 (0.7)
Missing/unknown, n (%)	36 (1.8)
WOMAC^a scores	
Pain [median (IQR)]	2 (5)
Charlson comorbidity index score^b [median (IQR)]	0 (1)
Current medication use at baseline	
Musculoskeletal analgesia (yes), n (%)^c	
COX-2	195 (9.7)
Opioid analgesics	103 (5.1)
NSAIDs	295 (14.7)
Paracetamol	77 (3.8)
CS	191 (9.5)
Osteoporosis-related medication (yes), n (%) ^c	219 (10.9)
Statins (yes), n (%) ^c	548 (27.4)
Anti-histamine (yes), n (%) ^c	208 (10.4)
Anti-depressants/anxiolytics/psychotropics (yes), n (%) ^c	281 (14.0)
Diabetes-related medication (yes), n (%)^c	
All diabetes-related medications ^d	139 (6.9)
Metformin	98 (4.9)
Anti-hypertensives (yes), n (%)^c	
Beta-adrenergic blockers	299 (14.9)
Angiotensin-converting enzyme inhibitor	301 (15.0)
Angiotensin receptor blockers	228 (11.4)
Calcium channel blockers	265 (13.2)
Radiographic measures	
Medial minimum JSW (mm)	3.47 (1.47)
Bilateral disease, n (%)	981 (49.0)
Radiographic alignment, n (%)	
Neutral	539 (26.9)
Varus	608 (30.4)
Valgus	848 (42.3)
Missing	8 (0.4)

All results presented as mean (s.d.) unless otherwise stated. ^aThe WOMAC score 0–20: 0=no pain and 20=most severe pain. ^bCharlson comorbidity score: 0–12, higher scores denote greater comorbidity. ^cCurrent use of medication at baseline in participants with baseline mJSW data. ^dAll diabetes-related medications' includes metformin. COX-2: cyclooxygenase-2; JSW: joint space width; IQR: interquartile range; mJSW: medial minimum joint space width.

current non-use ($b = -0.042$, 95% CI -0.08 , -0.0004), independent of baseline age, sex, BMI, race, mJSW,

WOMAC pain score, knee alignment and Charlson comorbidity score (see Table 2). That is, mJSW was -0.042 mm smaller in current users of NSAIDs vs current non-users. Compared with non-users, there was no statistically significant association between change in mJSW and current use of paracetamol ($b = -0.043$, 95% CI -0.12 , 0.03). There was no statistically significant association between change in mJSW and current use of COX-2 inhibitors ($b = -0.046$, 95% CI -0.13 , 0.035) and CS use ($b = -0.006$, 95% CI -0.06 , 0.04). In multivariate analysis, the use of opioid analgesia just failed to reach conventional levels of statistical significance ($b = -0.055$, 95% CI -0.11 , 0.002).

In multivariate analysis, there was no statistically significant association between change in mJSW and current use of osteoporosis-related medication ($b = 0.01$, 95% CI -0.05 , 0.07), statins ($b = -0.034$, 95% CI -0.08 , 0.01), anti-histamines ($b = 0.03$, 95% CI -0.03 , 0.09) and anti-depressants ($b = -0.048$, 95% CI -0.10 , 0.01) respectively. Moreover, we did not observe a relationship between change in mJSW and current use of diabetes-related medication ($b = -0.02$, 95% CI -0.05 , 0.1), comprising all diabetes-related medications, and in users of metformin ($b = 0.026$, 95% CI -0.05 , 0.1).

There was no statistically significant association between mJSW and use of beta-adrenergic blockers ($b = -0.02$, 95% CI -0.07 , -0.03), angiotensin-converting enzyme inhibitors ($b = -0.015$, 95% CI -0.06 , 0.03), angiotensin receptor blockers ($b = 0.026$, 95% CI -0.03 , 0.08) and calcium channel blockers ($b = -0.04$, 9% CI -0.09 , 0.01) (see supplementary Table S3, available at *Rheumatology* online).

In our sensitivity analysis, a comparison of participants included at 48 months' follow-up compared with those included at 72 months' follow-up showed that participants included at the later visits were older, did not show increased comorbidity, had significantly greater mJSW compared with participants at 48 months' follow-up (supplementary Table S4, available at *Rheumatology* online) and had less knee pain. Further, restricting the analysis to 48 months' follow-up showed that in multivariate analysis, osteoporosis-related medications were protective against the loss of mJSW ($b = 0.07$, 95% CI 0.01 , 0.14) compared with current non-users, calcium channel blockers were associated with the loss of mJSW ($b = -0.06$, 95% CI -0.12 , -0.005), and the relationship between current use of NSAIDs and mJSW change was lost (0.026 , 95% CI -0.02 , 0.07).

Discussion

Our study examined the relationship between current medication use, compared with current non-use, and change in radiographic medial mJSW in participants with RKOA across 8 years. Of seven specific medication classes specified *a priori*, mJSW was reduced in current users of NSAIDs ($b = -0.042$, 95% CI -0.08 , -0.0004) compared with current non-users.

TABLE 2 Effect estimates for the association of mJSW with medication use

Medication class/category	Outcome: medial minimum joint space width (mm)	
	Univariate	Multivariate model ^a
Musculoskeletal <u>analgesia</u>		
COX-2	-0.046 (-0.14, 0.05), 0.32	-0.046 (-0.13, 0.035), 0.27
Opioid analgesics	-0.076 (-0.14, -0.015), 0.015	-0.055 (-0.11, 0.002), 0.058
NSAIDs	-0.046 (-0.09, -0.001), 0.044	-0.042 (-0.08, -0.0004), 0.048
Paracetamol	-0.061 (-0.14, 0.017), 0.13	-0.043 (-0.12, 0.03), 0.25
CS	-0.021 (-0.08, 0.03), 0.45	-0.006 (-0.06, 0.04), 0.81
Osteoporosis-related medication	-0.018 (-0.09, 0.05), 0.61	0.01 (-0.05, 0.07), 0.75
Statins	-0.06 (-0.11, -0.01), 0.019	-0.034 (-0.08, 0.01), 0.11
Diabetes-related medication	0.009 (-0.09, 0.10), 0.86	0.02 (-0.05, 0.1), 0.56
Metformin	0.03 (-0.06, 0.12), 0.55	0.026 (-0.05, 0.1), 0.50
Anti-histamine medication	0.05 (-0.02, 0.11), 0.15	0.03 (-0.03, 0.09), 0.30
Anti-depressant/anxiolytics/ psychotropic medications	-0.09 (-0.16, -0.019), 0.012	-0.048 (-0.10, 0.01), 0.095
Anti-hypertensives		
Beta-adrenergic blockers	-0.03 (-0.09, -0.03), 0.25	-0.02 (-0.07, -0.03), 0.38
Angiotensin-converting enzyme inhibitor	-0.02 (-0.08, 0.03), 0.41	-0.015 (-0.06, 0.03), 0.53
Angiotensin receptor blockers	0.02 (-0.05, 0.08), 0.56	0.026 (-0.03, 0.08), 0.35
Calcium channel blockers	-0.04 (-0.1, 0.03), 0.24	-0.04 (-0.09, 0.01), 0.11

All results presented as unstandardized beta coefficients, 95% CI and *P*-values. Reference group: current non-users. Significant findings ($P \leq 0.05$) are shown in bold. ^aAdjusted for baseline mJSW, age, sex, race, BMI, WOMAC pain score, knee alignment and Charlson comorbidity score. mJSW: medial minimum joint space width; COX-2: cyclooxygenase-2 inhibitor.

Our findings for the use of NSAIDs are in keeping with previous data. For instance, in an exploratory analysis using a separate sample of the OAI, Driban *et al.* reported that consistent use of NSAIDs over 36 months in participants with RKOA showed a signal for a reduction in medial JSW in left (effect size: -0.71) and right (effect size: -1.59) knees compared with non-users [14]. A further study using a separate OAI sample identified a reduction in JSW in regular users of NSAIDs (vs non-regular use) over 4 years ($b = -0.05$, 95% CI -0.14, 0.04), though the relationship was not statistically significant [22]. Our study goes beyond these studies to examine the relationship between current NSAID use and change in mJSW across 96 months of follow-up. Evidence from *in vivo* and *in vitro* studies suggest that specific NSAIDs may inhibit the synthesis of matrix proteoglycans [49] by acting on enzymes involved in the biosynthesis of chondroitin sulfate [50], thereby leading to the increased vulnerability of chondrocytes and the degeneration of cartilage.

We did not observe a statistically significant relationship between current use of CS and progression of RKOA, though the direction of effect was in agreement with previous studies ($b = -0.006$, 95% CI -0.06, 0.04). In the study by Zeng *et al.* use of IA CS injections was associated with an increased risk of JSW worsening over 4 years of follow-up (hazard ratio 2.92, 95% CI 2.19, 3.90) compared with non-users [19]. Several differences exist between our study and that of Zeng *et al.*,

which could explain the conflicting data. Firstly, our study sample size was modestly greater ($N = 191$ vs 148), and we defined current use as 'use in the previous 30 days' whilst Zeng *et al.* defined current use as 'use in the last 6 months' [19]. This could have resulted in multiple doses being administered within 6 months, which was not accounted for, thus the relationship between CS use and structural progression may be dose-dependent, which could explain the absence of an association in our study. In addition, we adjusted for baseline severity of structural OA disease whilst Zeng *et al.* did not propensity-score match by OA severity. Consequently, changes in mJSW may have been over-estimated due to underlying OA disease, contributing to the magnitude of effect.

Furthermore, we did not observe an association between mJSW and diabetes-related medication use, and metformin use specifically. Wang *et al.* reported, using data from the OAI, that consistent use of metformin (two of four visits) was associated with a protective effect to cartilage volume measured on MRI [34]. This study was, however, limited by a small sample size ($N = 52$) compared with our study ($N = 98$), and only used MRI data from baseline and 48 months, whilst our study used data across seven visits totalling 8 years of follow-up, increasing study power. In addition, previous data from the OAI has suggested that use of H₁ anti-histamines is associated with reduced prevalence of RKOA compared with non-use [51]. This study was cross-sectional and

examined prevalence, whilst we examined change using data from multiple visits.

There are several strengths to this study. To our knowledge, this is the largest study to have examined the association between current medication use and change in mJSW in participants with RKOA, and to have utilized data across 8 years of follow-up. Whilst it has been previously reported that location-specific measures of medial JSW may demonstrate increased reproducibility [52] and may have improved accuracy in measuring OA progression [42] over more general measures of JSW, we used mJSW as our measure of progression. This is because the medial compartment is most commonly involved in the occurrence and progression of knee OA [53], and this measure has been routinely used in the assessment of disease progression [47, 54]. Joint replacement [55] and KL scoring have been proposed as alternative measures of progression, though loss of JSW is an accepted metric to assess longitudinal progression over time [56] and is more sensitive to change than a binary and ordinal score. Furthermore, we used prescribed medications, rather than non-prescribed medications, as our exposure since it has been shown that prescriptions are more reflective of regular use and clinically important doses [22], particularly over long periods of time. We do, however, acknowledge that use of over-the-counter medications, particular non-prescriptive analgesia, is common among OA patients and thus not accounting for this in our study is a limitation.

There are several potential limitations to this study. As with all previous observational medication-related studies, it is difficult to isolate the effect of medication on the outcome independent of the underlying disease and/or the presence of comorbidity. In our analysis, we tried to limit the effects of confounding by indication by adjusting for baseline severity of OA (as baseline mJSW); there is evidence to suggest that baseline joint health is associated with later progression [57]. We were, however, unable to adjust for the amount of time a participant had been diagnosed as RKOA-positive prior to study entry, as these data were not captured as part of the OAI protocol. Subsequently, we were unable to determine at baseline whether participants were slow, moderate or rapid progressors. Furthermore, we adjusted for baseline Charlson comorbidity score to limit the effects of comorbidity on the relationship between medication use and mJSW change. Whilst multivariate analysis adjusting for baseline severity of the target disease and pain can correct for confounding by indication to some extent, we acknowledge that our models may have been subject to residual confounding by indication, which may have persisted beyond our study design and statistical procedures. For instance, it is highly likely that patients with structural progression have more knee pain and are therefore more likely to use analgesics (i.e. CS) [58]. We performed multiple testing, which could have led to some of our observed, statistically significant findings. However, given that the results for the use of

NSAIDs remained statistically significant across both univariate and multivariate models, we have confidence that our findings were robust to type 2 error. In addition, we were unable to take account of medication dose in the analysis as these data were unavailable.

Our sensitivity analysis revealed that participants included at 48 months' follow-up compared with those included at 72 months' follow-up were older, had greater mJSW and had less knee pain. Whilst this was expected, it would suggest that, due to study design, this introduced 'missingness not at random'. Compared with baseline, there was a 54.53 and 53.70% reduction in study participants at 72 and 96 months, respectively. Despite this, we decided to include all available visits in our primary analysis, including the later visits (i.e. 72- and 96-month visits), to help increase the precision of our estimates. Loss of statistically significant findings for use of NSAIDs, and the change in the direction of the effect, was most likely due to the reduced study sample. Controlled clinical trials are needed to assess the disease-modifying effects of NSAIDs.

In this study, we observed a statistically significant association between current use of NSAIDs and loss of mJSW ($b = -0.042$, 95% CI -0.08 , -0.0004); however, it is unlikely that these changes are clinically relevant, as they fall short of conventional thresholds [59].

Conclusion

In this exploratory analysis, compared with current non-users, current use of prescription NSAIDs was associated with the loss of mJSW. Further studies are required, using clinical trial data, to confirm these findings.

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Data availability statement

All data generated and analysed in this study are available upon reasonable request. Access to data generated in this report should be sent to the corresponding author at thomas.perry@ndorms.ox.ac.uk.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393:1745–59.
- Cross M, Smith E, Hoy D *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1323–30.
- Lawrence RC, Felson DT, Helmick CG *et al.*; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
- Raynauld J-P, Martel-Pelletier J, Berthiaume M-J *et al.* Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. *Arthritis Res Ther* 2005;8:R21.
- Raynauld J-P, Martel-Pelletier J, Berthiaume M-J *et al.* Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum* 2004;50:476–87.
- Neogi T, Felson D, Niu J *et al.* Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* 2009;339:b2844.
- Bannuru RR, Osani MC, Vaysbrot EE *et al.* OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
- Bruyère O, Honvo G, Veronese N *et al.* An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Semin Arthritis Rheum* 2019;49:337–50.
- Fernandes L, Hagen KB, Bijlsma JWJ *et al.* EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–35.
- Jordan KM, Arden NK, Doherty M *et al.* EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;62:1145–55.
- Kolasinski SL, Neogi T, Hochberg MC *et al.* 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)* 2020; 72:149–62.
- McGrory B, Weber K, Lynott JA *et al.*; American Academy of Orthopaedic Surgeons. The American Academy of Orthopaedic Surgeons evidence-based clinical practice guideline on surgical management of osteoarthritis of the knee. *J Bone Joint Surg Am* 2016;98:688–92.
- Conaghan PG, Dickson J, Grant RL, Guideline Development Group. Care and management of osteoarthritis in adults: summary of NICE guidance. *Bmj* 2008;336:502–3.
- Driban JB, Lo GH, Eaton CB *et al.* Exploratory analysis of osteoarthritis progression among medication users: data from the osteoarthritis initiative. *Ther Adv Musculoskelet Dis* 2016;8:207–19.
- Mastbergen SC, Jansen NWD, Bijlsma JWJ, Lafeber FPJG. Differential direct effects of cyclo-oxygenase-1/2 inhibition on proteoglycan turnover of human osteoarthritic cartilage: an in vitro study. *Arthritis Res Ther* 2006;8:R2.
- Alvarez-Soria MA, Largo R, Santillana J *et al.* Long term NSAID treatment inhibits COX-2 synthesis in the knee synovial membrane of patients with osteoarthritis: differential proinflammatory cytokine profile between celecoxib and aceclofenac. *Ann Rheum Dis* 2006;65:998–1005.
- Nakata K, Hanai T, Take Y *et al.* Disease-modifying effects of COX-2 selective inhibitors and non-selective NSAIDs in osteoarthritis: a systematic review. *Osteoarthritis Cartilage* 2018;26:1263–73.
- Tellegen AR, Rudnik-Jansen I, Pouran B *et al.* Controlled release of celecoxib inhibits inflammation, bone cysts and osteophyte formation in a preclinical model of osteoarthritis. *Drug Deliv* 2018;25:1438–47.

- 19 Zeng C, Lane NE, Hunter DJ *et al.* Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2019;27:855–62.
- 20 McAlindon TE, LaValley MP, Harvey WF *et al.* Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017;317:1967–75.
- 21 Hafezi-Nejad N, Guermazi A, Roemer FW *et al.* Long term use of analgesics and risk of osteoarthritis progressions and knee replacement: propensity score matched cohort analysis of data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2016; 24:597–604.
- 22 Lapane KL, Yang S, Driban JB *et al.* Effects of prescription nonsteroidal antiinflammatory drugs on symptoms and disease progression among patients with knee osteoarthritis. *Arthritis Rheumatol* 2015;67: 724–32.
- 23 Martel-Pelletier J, Roubille C, Abram F *et al.* First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. *Ann Rheum Dis* 2015;74:547–56.
- 24 Gonzalez-Fuentes AM, Green DM, Rossen RD, Ng B. Intra-articular hyaluronic acid increases cartilage breakdown biomarker in patients with knee osteoarthritis. *Clin Rheumatol* 2010;29:619–24.
- 25 Raynaud J-P, Buckland-Wright C, Ward R *et al.* Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2003;48:370–7.
- 26 Jones A, Doherty M. Intra-articular corticosteroids are effective in osteoarthritis but there are no clinical predictors of response. *Ann Rheum Dis* 1996;55:829–32.
- 27 Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consultants in England and Wales. *Ann Rheum Dis* 2004;63:408–14.
- 28 Marshall DA, Liu X, Barnabe C *et al.* Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada. *BMJ Open* 2019;9:e033334.
- 29 Swain S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in osteoarthritis: a systematic review and meta-analysis of observational studies. *Arthritis Care Res (Hoboken)* 2020;72:991–1000.
- 30 Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD Open* 2015;1: e000077.
- 31 Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. *Postgrad Med J* 2012;88:240–2.
- 32 Leung Y-Y, Allen JC, Ang L-W, Yuan J-M, Koh W-P. Diabetes mellitus and the risk of total knee replacement among Chinese in Singapore, the Singapore Chinese Health Study. *Sci Rep* 2017;7:40671.
- 33 Shirinsky IV, Shirinsky VS. Effects of medication-treated diabetes on incidence and progression of knee osteoarthritis: a longitudinal analysis of the osteoarthritis initiative data. *Rheumatol Int* 2017;37:983–91.
- 34 Wang Y, Hussain SM, Wluka AE *et al.* Association between metformin use and disease progression in obese people with knee osteoarthritis: data from the Osteoarthritis Initiative—a prospective cohort study. *Arthritis Res Ther* 2019;21:127.
- 35 Kang KY, Kim Y-K, Yi H, Kim J *et al.* Metformin downregulates Th17 cells differentiation and attenuates murine autoimmune arthritis. *Int Immunopharmacol* 2013;16:85–92.
- 36 Ashmeik W, Joseph GB, Nevitt MC *et al.* Association of blood pressure with knee cartilage composition and structural knee abnormalities: data from the osteoarthritis initiative. *Skeletal Radiol* 2020;49:1359–68.
- 37 Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol* 2012;8:729–37.
- 38 Lo GH, McAlindon TE, Katz JN *et al.* Systolic and pulse pressure associate with incident knee osteoarthritis: data from the osteoarthritis initiative. *Clin Rheumatol* 2017;36: 2121–8.
- 39 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494–502.
- 40 Synarc. Radiographic procedure manual for examinations of the knee, hand, pelvis and lower limbs. Osteoarthritis initiative: a knee health study. 2006; <https://oai.epi-ucsf.org/datarelease/operationsManuals/RadiographicManual.pdf> (2 November 2020, date last accessed).
- 41 Nevitt MF, Felson DT, Lester G. The osteoarthritis initiative: protocol for the cohort study. 2017; <https://oai.epi-ucsf.org/datarelease/About.asp> (2 November 2020, date last accessed).
- 42 Neumann G, Hunter D, Nevitt M *et al.* Location specific radiographic joint space width for osteoarthritis progression. *Osteoarthritis Cartilage* 2009;17:761–5.
- 43 Duryea J, Li J, Peterfy CG, Gordon C, Genant HK. Trainable rule-based algorithm for the measurement of joint space width in digital radiographic images of the knee. *Med Phys* 2000;27:580–91.
- 44 Pahor M, Chrischilles EA, Guralnik JM *et al.* Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol* 1994;10:405–11.
- 45 Ratzlaff C, Ashbeck EL, Guermazi A *et al.* A quantitative metric for knee osteoarthritis: reference values of joint space loss. *Osteoarthritis Cartilage* 2018;26:1215–24.
- 46 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- 47 Halilaj E, Le Y, Hicks JL, Hastie TJ, Delp SL. Modeling and predicting osteoarthritis progression: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2018;26: 1643–50.
- 48 Kingsbury SR, Hensor EMA, Walsh CAE, Hochberg MC, Conaghan PG. How do people with knee osteoarthritis use osteoarthritis pain medications and does this change over time? Data from the Osteoarthritis Initiative. *Arthritis Res Ther* 2013;15:R106.

- 49 Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and in vivo. *Am J Med* 1987;83:29–34.
- 50 Hugenberg ST, Brandt KD, Cole CA. Effect of sodium salicylate, aspirin, and ibuprofen on enzymes required by the chondrocyte for synthesis of chondroitin sulfate. *J Rheumatol* 1993;20:2128–33.
- 51 Shirinsky I, Shirinsky V. H1-antihistamines are associated with lower prevalence of radiographic knee osteoarthritis: a cross-sectional analysis of the Osteoarthritis Initiative data. *Arthritis Res Ther* 2018;20:116.
- 52 Duryea J, Zaim S, Genant HK. New radiographic-based surrogate outcome measures for osteoarthritis of the knee. *Osteoarthritis Cartilage* 2003;11:102–10.
- 53 Murray CJL, Vos T, Lozano R *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2197–223.
- 54 Benichou OD, Hunter DJ, Nelson DR *et al.* One-year change in radiographic joint space width in patients with unilateral joint space narrowing: data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)* 2010;62:924–31.
- 55 Altman RD, Abadie E, Avouac B *et al.* Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. *Osteoarthritis Cartilage* 2005;13:13–9.
- 56 Hunter DJ, Le Graverand M-PH, Eckstein F. Radiologic markers of osteoarthritis progression. *Curr Opin Rheumatol* 2009;21:110–7.
- 57 Lo GH, Schneider E, Driban JB *et al.* Periarticular bone predicts knee osteoarthritis progression: data from the osteoarthritis initiative. *Semin Arthritis Rheum* 2018;48:155–61.
- 58 Conaghan PG. Corticosteroids and osteoarthritis progression: a confounded issue. *Osteoarthritis Cartilage* 2019;27:e5–6.
- 59 Ornetti P, Brandt K, Hellio-Le Graverand MP *et al.* OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. *Osteoarthritis Cartilage* 2009;17:856–63.