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Prevalence of Nonsteroidal Antiinflammatory Drugs Prescribed for Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies

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Objective. Our systematic review aimed to investigate the proportion of participants with osteoarthritis who were prescribed nonsteroidal antiinflammatory drugs (NSAIDs) by their health care provider.

Methods. Electronic databases were searched for observational studies reporting NSAID prescribing to participants with diagnosed osteoarthritis of any region. Risk of bias was assessed using a tool designed for observational studies measuring prevalence. Random and fixed-effects meta-analysis was used. Meta-regression investigated study-level factors associated with prescribing. The overall evidence quality was assessed using Grading of Recommendations Assessment, Development, and Evaluation criteria.

Results. Fifty-one studies were included, published between 1989 and 2022, with 6,494,509 participants. The mean age of participants was 64.7 years (95% confidence interval [95% CI] 62.4, 67.0; n = 34 studies). Most studies were from Europe and Central Asia (n = 23 studies), and North America (n = 12 studies). Most studies were judged to be at low risk of bias (75%). Heterogeneity was eliminated when removing studies with a high risk of bias, to give a pooled estimate of NSAIDs prescribing to participants with osteoarthritis of 43.8% (95% CI 36.8, 51.1; moderate quality of evidence). Meta-regression determined that prescribing was associated with year (decreased prescribing over time; $P = 0.05$) and geographic region ($P = 0.03$; higher in Europe and Central Asia and in South Asia than in North America) but not with clinical setting.

Conclusion. Data from over 6.4 million participants with osteoarthritis between 1989 and 2022 indicate that NSAID prescribing has decreased over time and that prescribing differs between geographic locations.

INTRODUCTION

Osteoarthritis is the most common type of arthritis (1). Clinical guidelines for the management of osteoarthritis recommend nonpharmacologic treatments, such as educational, psychosocial, and physical interventions, as well as pharmacologic management such as topical and oral nonsteroidal antiinflammatory drugs (NSAIDs) (2,3). NSAIDs have been shown, through meta-analyses, to be effective in achieving clinical improvements in pain and function (4,5) in people with osteoarthritis symptoms and are recommended as an effective symptomatic treatment for early arthritis in some guidelines (2,6). Guidelines frequently recommend NSAIDs to be prescribed at the smallest effective dose for the shortest possible time (2,6). Although NSAIDs can be a less costly management strategy than conservative care (e.g., ongoing physical therapy) they are not without risk of harm (4,5). Caution should be taken in prescribing NSAIDs for use in people with a high risk of diabetes mellitus, hypertension, renal impairment, and heart disease (7,8), with consideration that cyclooxygenase 2 (COX-2) selective NSAIDs are associated with fewer gastrointestinal ulcers and complications than nonselective NSAIDs (9,10).

The incidence of NSAIDs use for the management of osteoarthritis is common as evidenced by numerous individual studies (11,12). However, the extent to which NSAIDs are prescribed for osteoarthritis globally and what factors may be associated with prescribing are unclear. Previous systematic reviews related to osteoarthritis have focused on clinical outcomes such as efficacy

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SIGNIFICANCE & INNOVATIONS

- This is the first review to assess changes in, and factors associated with, nonsteroidal antiinflammatory drugs (NSAIDs) prescribing for osteoarthritis.
- This large review analyzed data from observational studies of 6,494,509 participants between 1989 and 2022.
- NSAID prescribing for osteoarthritis decreased over time and was associated with geographic region but not with clinical setting.

and safety of NSAIDs (13–16). Previous studies have suggested that both oral and topical NSAIDs exhibit pain relief among people with osteoarthritis (4), but topical NSAIDs had a lower risk of toxicity (13), while there is no difference in efficacy between selective and nonselective NSAIDs in reducing pain and improving function (17). However, the prevalence of NSAID prescribing for the clinical management of osteoarthritis is unclear, and little is known about prescribing practices across countries and any differences in the management of regional types of osteoarthritis. Understanding to what extent NSAIDs are prescribed for osteoarthritis will determine any differences in prescribing and provide a benchmark for future studies. Therefore, this systematic review aimed to investigate the proportion of participants with osteoarthritis who were prescribed an NSAID by their health care provider, factors associated with prescribing, and geographic differences in prescribing.

MATERIALS AND METHODS

Eligibility criteria. The protocol for this review was devised in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (18) and was registered on PROSPERO (CRD42021238699; www.crd.york.ac.uk). We included observational studies (cross-sectional, prospective, or retrospective cohort or case–control studies) of adults (age ≥18 years) with clinician-diagnosed osteoarthritis at any site, and who were prescribed an NSAID to manage their osteoarthritis symptoms. We included pharmacy dispensing data provided that the data were specific for clinician-diagnosed osteoarthritis and for which NSAIDs were prescribed. We excluded studies that did not include the representative population sample (e.g., not consecutive cases or randomly sampled), studies of self-reported NSAID use, over-the-counter supply of NSAIDs, and those with self-reported osteoarthritis diagnoses.

Search strategy. We searched the following electronic databases: PubMed (National Library of Medicine database), MEDLINE, EMBASE, and International Pharmaceutical Abstracts (the latter 3 from OvidSP), and Web of Science (Thomson Reuters) on April 23, 2022. We conducted backward and forward author and reference citation tracking of included articles and communicated with content experts to identify any missing studies. Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157, contains the details of the search strategy.

Screening. Two authors from a panel (ZY, SM, or SK) independently screened records against the eligibility criteria. Duplicate studies were removed manually and using the automated function in Endnote. Disagreements were resolved first by discussion, then by arbitration with an independent third review author if needed. For articles written in languages that the review authors could not read, we asked colleagues to assist with reading and appraising the article.

Data extraction and management. Two review authors independently extracted data from eligible studies using a piloted, standardized extraction form in Excel (ZY and SM). Disagreements were resolved first by discussion, then by arbitration with an independent third review author if needed (CAS and AJM). We contacted the authors of studies for clarification and additional data if relevant data were missing. Information extracted included bibliometric data (authors, title, year of publication, language, funding sources), study characteristics (study design, data source, sample size, sampling dates and methods, country), participants (age, sex, site of diagnosis, symptom duration, first or ongoing presentation of index visit), pain intensity (e.g., numerical pain rating scale), interventions (profession of prescribing clinician, the number of NSAIDs prescribed or dispensed on prescription, dose, mode of delivery, frequency, duration; the proportion of other medicines and nonpharmacologic therapies coprescribed with the NSAIDs), and data completeness (i.e., the percentage of missing data, how missing data were handled).

Medicines were categorized using the Anatomical Therapeutic Chemical classification system (19), and NSAIDs were classed as nonselective or COX-2 selective, followed by the mode of delivery. A list of nonselective and COX-2 selective NSAIDs is in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157. Combination medicines were initially classified by the NSAIDs. Data on co-administered therapy were retrieved if the therapy was prescribed to alleviate osteoarthritis and coprescribed with an NSAID. Nonpharmacologic treatments were categorized based on the therapies (e.g., physical therapy).

Countries were grouped according to World Health Organization (WHO) regions (East Asia and Pacific, Europe and Central Asia, Latin America and Caribbean, Middle East and North Africa, North America, South Asia) (20) and income status (low-, middle- and high-income) as per the World Bank (21).

Risk-of-bias assessment. Risk of bias was assessed using the tool developed by Hoy et al (22) to assess the risk of bias

in observational studies that measure prevalence. A study's overall risk of bias was low if further research was very unlikely to change our confidence in the estimate, moderate if further research was likely to have an important impact on our confidence in the estimate and may change the estimate, or high if further research was very likely to have an important impact on our confidence in the estimate and was likely to change the estimate (22). The criteria for the risk-of-bias assessment are shown in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

Data synthesis. Study characteristics and study participants are descriptively reported. Random and fixed-effects meta-analyses were used to pool the main prevalence estimate and random effects were used for the subgroup analyses. Statistical heterogeneity among the studies was assessed using a visual inspection of the forest plot and I^2 statistics following the recommended guide for interpretation of I^2 as 0–40% = might not be important, 30–60% = may represent moderate heterogeneity, 50–90% = may represent substantial heterogeneity, and 75–100% = considerable heterogeneity (23). Meta-regression analyses were performed to explore sources of heterogeneity across the included studies and to determine possible study-related factors associated with prescribing. Factors included the WHO region (compared to North America), sampling year (continuous; defined as the year associated with the midpoint of the prevalence sampling period), setting (primary care, tertiary care, multiple clinical settings, population based, compared database [e.g., prescribing database, dispensing claims database]), the duration of the prevalence period (continuous in months), and whether funding was reported (compared to none). Analyses were conducted in Comprehensive Meta-Analysis, version 3.3.070. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (24) was used to assess the quality of the evidence. Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157 contains the details of GRADE criteria.

Subgroup and sensitivity analyses. We conducted 4 planned subgroup analyses to 1) investigate differences in pooled prescribing estimates per osteoarthritis site, including participants with spinal-related osteoarthritis, 2) compare the pooled prescribing estimates per WHO geographic region and country income status, 3) determine the proportion of participants using different types of NSAIDs and dose, including grouped per nonselective and COX-2 selective NSAIDs, and 4) determine the differences in the proportion of participants prescribed NSAIDs per mode of delivery (i.e., topical) and action. Sensitivity analysis was performed as there was an adequate number of studies (>10 studies) by excluding studies assessed to have high risk of bias and then repeating the analyses.

RESULTS

A total of 9,220 records were identified by searching electronic databases, plus 10 additional articles were identified through citation tracking. Fifty-one studies met the inclusion criteria and were included in this review. The flow of studies is shown in Figure 1.

The 51 studies provided data on a total of 6,494,509 participants with a mean age of 64.7 years (95% confidence interval [95% CI] 62.4, 67.0; n = 34 studies) (11,12,25–55). The included studies were published between 1989 and 2022 and were all in English except 1 study published in Croatian (56). Studies were from 31 countries across the globe, including South Asia (n = 4 studies) (37,47,49,57), Middle East and North Africa (n = 1 study) (33), East Asia and Pacific (n = 10 studies) (12,25,32,38,40,51,53,58–60), Europe and Central Asia (n = 23 studies) (26–29,39,42,43,45,46,48,50,52,54–56,61–68), Latin America and Caribbean (n = 1 study) (44), and North America (n = 12 studies) (11,30,31,34–36,41,69–73). Most studies (90.2%) were from high-income countries with 1 study from an upper-middle income country (44), and 4 studies were from lower-middle income countries (37,47,49,57). Half the studies (52.9%) were from clinical settings, with 20 studies from primary care (26,28,29,34,39,42,46,48–50,52,54,55,58,60,64,65–68), 7 studies from tertiary care clinics (37,43,44,47,56,57,72), and 5 studies from multiple care (30,31,41,45,62); 18 studies (35%) provided prevalence data from a database (11,12,25,27,32,33,35,36,38,40,51,53,59,63,69–71,73), and 1 was a population-based study (61). Characteristics of included studies are shown in Table 1. No study reported the coprescribing of analgesic drugs or nonpharmacologic therapies specifically occurring at the same time of NSAID prescribing. However, 26 studies reported that participants used other medicines (12,25,27,28,31,33–36,42–45,48,51–53,59,60,62,66–68,70,72) or physical therapy (32,45,58,60,70) at some time during the sampling period.

Risk of bias. The majority of studies (75%) were judged to be at low risk of bias. Eight studies (30,37,43,56,57,61,66,72) were classified as having a moderate risk of bias (16%), while 5 studies (46–48,67,69) were scored as having a high risk of bias (9%). The domain that most frequently scored poorly was related to using validated outcome measures, as most studies evaluated clinical records. Only 5% of studies collected data using validated measures. The risk-of-bias scores are shown in Table 2.

Proportion of patients with osteoarthritis who were prescribed NSAIDs. High heterogeneity was present when pooling NSAID prescribing estimates across all studies (I^2 = 99.9%). A forest plot of individual studies is shown in Figure 2. We conducted a sensitivity analysis to explore heterogeneity related to risk of bias. When studies scored as having a high

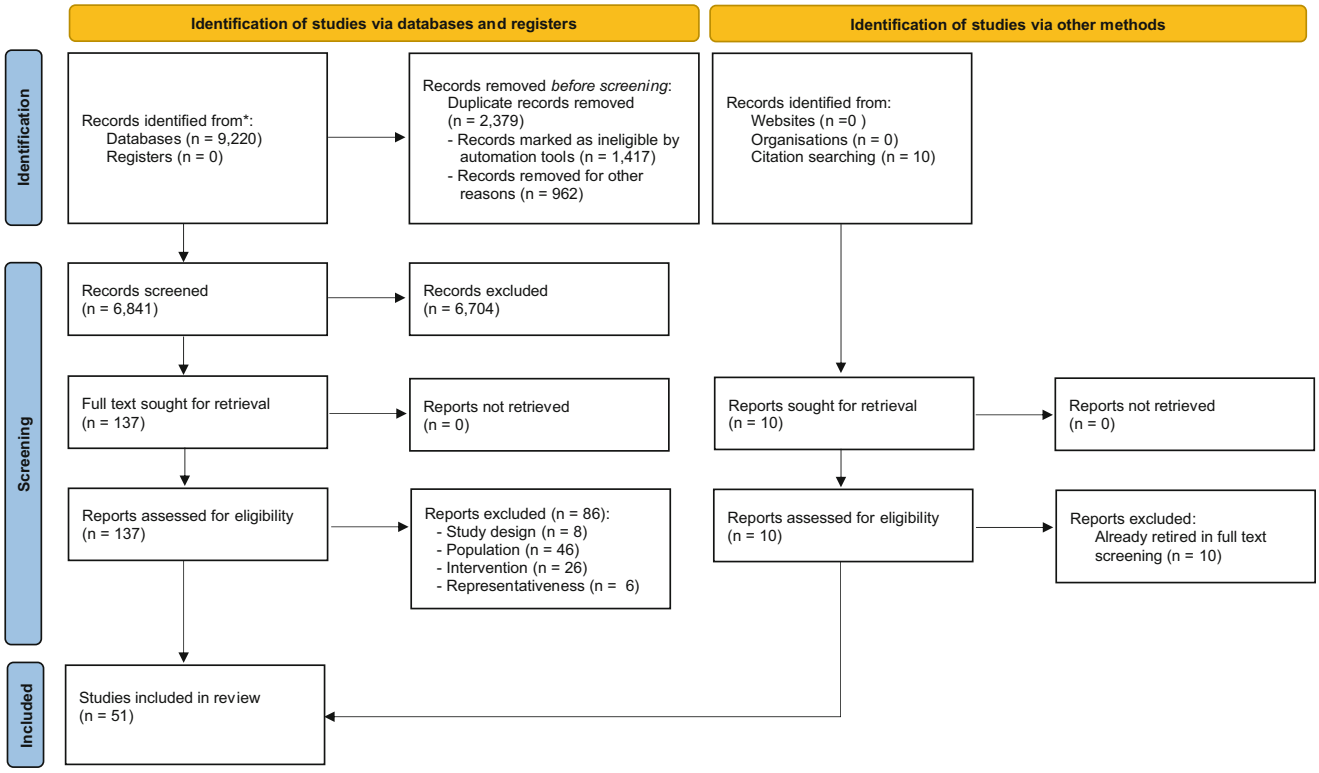

Figure 1. Study flow diagram.

risk of bias were removed (n = 5 studies) (46–48,67,69), the pooled prescribing estimate remained similar (43.8% [95% CI 36.8, 51.1], n = 46 studies, high quality of evidence I^2 = 5.1%) (11,12,25,26,28–46,49–56,58–61,58–64,65,66,68,70–73) compared to the original estimate with high heterogeneity (43.1% [95% CI 36.3, 50.1], n = 51 studies, I^2 = 99.9%, low quality of evidence). A post hoc sensitivity analysis was conducted to explore the primary analyses using an alternative statistical approach (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157), which resulted in less conservative estimates than our original model.

Factors associated with prescribing of NSAIDs. Meta-regression was used to explore potential sources of heterogeneity and to determine potential factors associated with prescribing. Meta-regression analyses of study-related factors explained 42% of heterogeneity (R^2 = 0.42). Prescribing was associated with the WHO region (*P* = 0.026), with increased prescribing in the regions of East Asia and Pacific (coefficient 0.86 [95% CI –0.098, 1.81]; *P* = 0.078), Europe and Central Asia (coefficient 1.26 [95% CI 0.23, 2.28]; *P* = 0.02), Latin America and Caribbean (coefficient 2.02 [95% CI –0.62, 4.65]; *P* = 0.13), Middle East and North Africa (coefficient 0.26 [95% CI –2.11, 2.63]; *P* = 0.83), and South Asia (coefficient 3.02 [95% CI 1.27, 4.76]; *P* = 0.001), compared to North America (US and Canada). There was a decrease in NSAID prescribing over time (coefficient –0.04 [95% CI –0.08, 0.00]; *P* = 0.05) and longer sampling duration (coefficient –0.006 [95% CI –0.009, –0.002]; *P* = 0.001). Reporting of funding (*P* = 0.59) and clinical setting (*P* = 0.20) did not influence prescribing. A summary of the meta-regression analysis is shown in Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

Subgroup analyses. *The proportion of NSAIDs prescribed to participants per osteoarthritis site.* The pooled estimate of NSAIDs prescribed to patients with hip osteoarthritis (27,32,60) was 34.9% (95% CI 23.8, 47.9; n = 3 studies, I^2 = 0%, high quality of evidence). In contrast, NSAID prescribing to patients with knee osteoarthritis was 46.3% (95% CI 36.9, 55.9; n = 11 studies, I^2 = 28.8%, moderate quality of evidence) (27,29,32,45,47,48,57,59,60,66,67) and for spine osteoarthritis was 66.9% (95% CI 66.6, 67.2; n = 1 study, I^2 = 0%, high quality of evidence) (27). The stratified analyses results are summarized in Table 3 and the forest plot shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

Prescribing estimates across WHO regions. The pooled prevalence of NSAIDs varied widely across geographical locations. The pooled estimate of NSAIDs prescribing was highest in South Asia at 83.4% (95% CI 74.8, 89.4; n = 4 studies, I^2 = 3.0%, moderate quality of evidence) (37,47,49,57), followed by Latin America and

Table 1. Characteristics of included studies*

Author, year (ref.)	Prevalence type	Setting	Country	OA sample size	OA site	Radiologic diagnosis	Age, mean ± SD years
Akazawa et al, 2019 (25)	Retrospective	Database	Japan	118,996	All regions	No	68.8 ± 13.1
Alacqua et al, 2008 (68)	Retrospective	Primary	Italy	142,346	All regions	No	NR
Arboleya et al, 2003 (26)	Retrospective	Primary	Spain	897	All regions	Yes	66.0 ± 9.0
Barcella et al, 2019 (27)	Retrospective	Database	Denmark	533,502	All regions	No	62.2 ± 14.3
Bennell et al, 2021 (60)	Retrospective	Primary	Australia	9,812	Hip/knee	No	NR
Castaño Carou et al, 2015 (28)	Prospective	Primary	Spain	1,258	Hip, knee, and hand	Yes	68 ± 9.5
Chandan et al, 2021 (55)	Retrospective	Primary	UK	25,659	All regions	No	68.53 ± 11.0
Colombo et al, 2021 (54)	Retrospective	Primary	Italy	71,467	All regions	No	71.36 ± 12.2
Cunnington et al, 2008 (73)	Retrospective	Database	US	80,826	All regions	No	NR
Denoeud et al, 2005 (29)	Prospective	Primary	France	2,430	Knee	Yes	66.8 ± 10.6
Dominick et al, 2003 (30)	Retrospective	Multiple	US	2,473	All regions	No	61.1 ± 14.0
Dominick et al, 2003 (31)	Retrospective	Multiple	US	11,298	All regions	No	80.2 ± 6.9
Ebata-Kogure et al, 2020 (32)	Retrospective	Database	Japan	328,631	Hip/knee	No	69.7 ± 11.5
Fallach et al, 2021 (33)	Retrospective	Database	Israel	180,126	All regions	No	58.5 ± 11.9
Gore et al, 2011 (35)	Retrospective	Database	US	207,010	All regions	Yes	53.2 ± 9.8
Gore et al, 2011 (36)	Retrospective	Database	US	112,951	All regions	Yes	56.9 ± 9.5
Gore et al, 2012 (34)	Retrospective	Primary	UK	18,184	All regions	No	70.6 ± 11.0
Gupta et al, 2018 (37)	Prospective	Tertiary	India	188	All regions	No	61.7 ± 6.9
Barbero et al, 2017 (67)	Prospective	Primary	Spain	646	Knee	No	NR
Hsu et al, 2017 (38)	Retrospective	Database	China (Taiwan)	43,635	All regions	No	60 ± 14.1
Jackson et al, 2017 (39)	Prospective	Primary	UK	1,724	All regions	No	66.1 ± 11.9
Kanneppady et al, 2017 (72)	Retrospective	Tertiary	US	296	All regions	No	47.5 ± NR
Kikuchi et al, 2021 (40)	Retrospective	Database	Japan	180,371	All regions	No	49.3 ± 11.8
Lanas et al, 2011 (62)	Prospective	Multiple	Spain	17,105	All regions	No	NR
Li et al, 2022 (71)	Retrospective	Database	Canada	100,358	All regions	No	68 ± NR
McDonald and Walsh, 2012 (41)	Retrospective	Multiple	US	128	All regions	No	74.1 ± 8.3
Patel et al, 2020 (70)	Retrospective	Database	US	44,990	All regions	No	75.9 ± NR
Paterson et al, 2018 (58)	Retrospective	Primary	Australia	621	Foot/ankle	No	NR
Pontes et al, 2018 (42)	Retrospective	Primary	Spain	22,652	All regions	No	75.6 ± 9.82
Rajamäki et al, 2019 (43)	Retrospective	Tertiary	Finland	13,739	All regions	No	68.7 ± 10.1
Reginato et al, 2015 (41)	Prospective	Tertiary	13 Latin American countries	3,040	All regions	Yes	62.5 ± 10.5
Reijman et al, 2005 (61)	Prospective	Population	Netherlands	3,585	Hip/knee	Yes	66 ± 6.9
Richette et al, 2011 (45)	Prospective	Multiple	France	1,821	Knee	Yes	67.3 ± 9.7
Russo et al, 2003 (65)	Retrospective	Primary	Italy	3,090	All regions	No	NR
Sakai et al, 2019 (59)	Retrospective	Database	Korea/Japan	1,143,636	Knee	No	NR
Shelbaya et al, 2018 (11)	Retrospective	Database	US	1,610,375	All regions	No	61 ± 12.2
Spitaels et al, 2020 (66)	Prospective	Primary	Belgium	1,595	Knee	No	55.3 ± NR
Spitaels et al, 2020 (66)	Prospective	Primary	Belgium	5,049	Knee	No	56.9 ± NR
Stambuk et al, 1989 (56)	Retrospective	Tertiary	Croatia	50	Hip	No	NR
Subramanian et al, 2020 (57)	Prospective	Tertiary	India	256	Knee	Yes	NR
Summanen et al, 2021 (46)	Retrospective	Primary	Finland	51,608	Hip/knee	No	56.6 ± 10.1
Togo et al, 2022 (53)	Retrospective	Database	Japan	114,078	All regions	No	70.9 ± 12.1
Tomeczkowski et al, 2014 (63)	Retrospective	Database	Germany	163,800	All regions	No	NR
Ullal et al, 2010 (47)	Retrospective	Tertiary	US	154	Knee	No	62.3 ± 7.8
Milano et al, 2016 (48)	Prospective	Primary	Spain	1,152	Knee	No	67.9 ± 6.8
Wang et al, 2019 (49)	Retrospective	Primary	China	212,546	All regions	No	65.5 ± 8.1
Wilson et al, 2015 (50)	Retrospective	Primary	Spain	238,536	All regions	No	67 ± 12.0
Wu et al, 2012 (69)	Retrospective	Database	US	96,666	All regions	No	65.2 ± NR
Xue et al, 2018 (12)	Retrospective	Database	China (Taiwan)	3,4338	All regions	No	61.9 ± 8.2
Yeh et al, 2021 (51)	Retrospective	Database	China (Taiwan)	13,520	All regions	No	50.1 ± 12.7
Yu et al, 2017 (64)	Retrospective	Primary	UK	432,343	All regions	Yes	67.2 ± NR
Zeng et al, 2019 (52)	Retrospective	Primary	UK	88,902	Knee, hip, and hand	No	70.1 ± 9.5

* NR = not reported; OA = osteoarthritis; ref. = reference.

Caribbean at 68.5% (95% CI 66.8, 70.1; n = 1 study, I^2 = 0%, high quality of evidence) (33), East Asia and Pacific at 46.8% (95% CI 35.0, 58.9; n = 10 studies, I^2 = 31.7%, high quality of evidence) (12,25,32,38,40,51,53,58–60), Europe and Central Asia at 40.2% (95% CI 31.8, 49.3; n = 23 studies, I^2 = 12.2%, moderate quality of evidence) (26,27,28,29,39,42,43,45,46,48,50,52,54–56,61–68), Middle East and North Africa at 34.1% (95% CI 33.9, 34.3; n = 1 study, I^2 = 0%, high quality of evidence) (44), and North America at 32.6% (95% CI 16.9, 53.6; n = 12 studies, I^2 = 11.0%, moderate quality of evidence) (11,30,31,34–36,41,69–73). The stratified

Table 2. Risk of bias scores*

Author, year (ref.)	1. Target population a close representation of the national population?	2. The sampling frame a representation of the target population?	3. Was random selection or census used to select the sample?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects?	6. Was an acceptable case definition used?	7. Was a valid/ reliable instrument used to measure the parameter of interest?	8. Was the same mode of data collection used?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Appropriate numerators and denominators used?	11. Overall score
Akazawa et al, 2019 (25)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Alacqua et al, 2008 (68)	Low	High	Low	Low	Low	Low	High	Low	Low	Low	Low
Arboleya et al, 2003 (26)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Barcella et al, 2019 (27)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Bennell et al, 2021 (60)	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Castaño Carou et al, 2015 (28)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Chandan et al, 2021 (55)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Colombo et al, 2021 (54)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Cunnington et al, 2008 (73)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Denoeud et al, 2005 (29)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Dominick et al, 2003 (30)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Dominick et al, 2003 (31)	Low	High	Low	Low	Low	Low	High	Low	High	Low	Moderate
Ebata-Kogure et al, 2020 (32)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Fallach et al, 2021 (33)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Gore et al, 2011 (35)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Gore et al, 2011 (36)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Gore et al, 2012 (34)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Gupta et al, 2018 (37)	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Barbero et al, 2017 (67)	High	High	High	High	High	High	High	Low	Low	Low	High

(Continued)

Table 2. (*Cont'd*)

Author, year (ref.)	1. Target population a close representation of the national population?	2. The sampling frame a representation of the target population?	3. Was random selection or census used to select the sample?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects?	6. Was an acceptable case definition used?	7. Was a valid/ reliable instrument used to measure the parameter of interest?	8. Was the same mode of data collection used?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Appropriate numerators and denominators used?	11. Overall score
Hsu et al, 2017 (38)	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low
Jackson et al, 2017 (39)	Low	High	Low	Low	Low	Low	High	Low	Low	Low	Low
Kanneppady et al, 2017 (72)	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Kikuchi et al, 2021 (40)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Lanas et al, 2011 (62)	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low
Li et al, 2022 (71)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
McDonald and Walsh, 2012 (41)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Patel et al, 2020 (70)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Paterson et al, 2018 (58)	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pontes et al, 2018 (42)	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Rajamäki et al, 2019 (43)	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Reginato et al, 2015 (41)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Reijman et al, 2005 (61)	High	High	Low	Low	Low	Low	High	Low	Low	Low	Moderate
Richette et al, 2011 (45)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Russo et al, 2003 (65)	Low	High	Low	Low	Low	Low	High	Low	Low	Low	Low
Sakai et al, 2019 (59)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Shelbaya et al, 2018 (11)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Spitaels et al, 2020 (66)	High	High	Low	Low	Low	Low	High	Low	Low	Low	Moderate
Stambuk et al, 1989 (56)	Low	High	Low	Low	Low	High	High	Low	Low	Low	Moderate
Subramanian et al, 2020 (57)	High	High	Low	Low	Low	Low	High	Low	Low	Low	Moderate

(Continued)

Table 2. (*Cont'd*)

Author, year (ref.)	1. Target population a close representation of the national population?	2. The sampling frame a representation of the target population?	3. Was random selection or census used to select the sample?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects?	6. Was an acceptable case definition used?	7. Was a valid/ reliable instrument used to measure the parameter of interest?	8. Was the same mode of data collection used?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Appropriate numerators and denominators used?	11. Overall score
Summanen et al, 2021 (46)	High	Low	Low	High	Low	Low	High	High	Low	Low	High
Togo et al, 2022 (53)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Tomeczkowski et al, 2014 (63)	Low	Low	Low	High	Low	Low	High	Low	Low	Low	Low
Ullal et al, 2010 (47)	High	High	Low	Low	Low	High	High	Low	Low	Low	High
Milano et al, 2016 (48)	High	High	High	High	High	High	High	High	Low	Low	High
Wang et al, 2019 (49)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Wilson et al, 2015 (50)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Wu et al, 2012 (69)	Low	Low	Low	High	Low	High	High	High	Low	Low	High
Xue et al, 2018 (12)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Yeh et al, 2021 (51)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Yu et al, 2017 (64)	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Zeng et al, 2019 (52)	High	Low	Low	Low	Low	Low	High	Low	Low	Low	Low

* Ref. = reference.

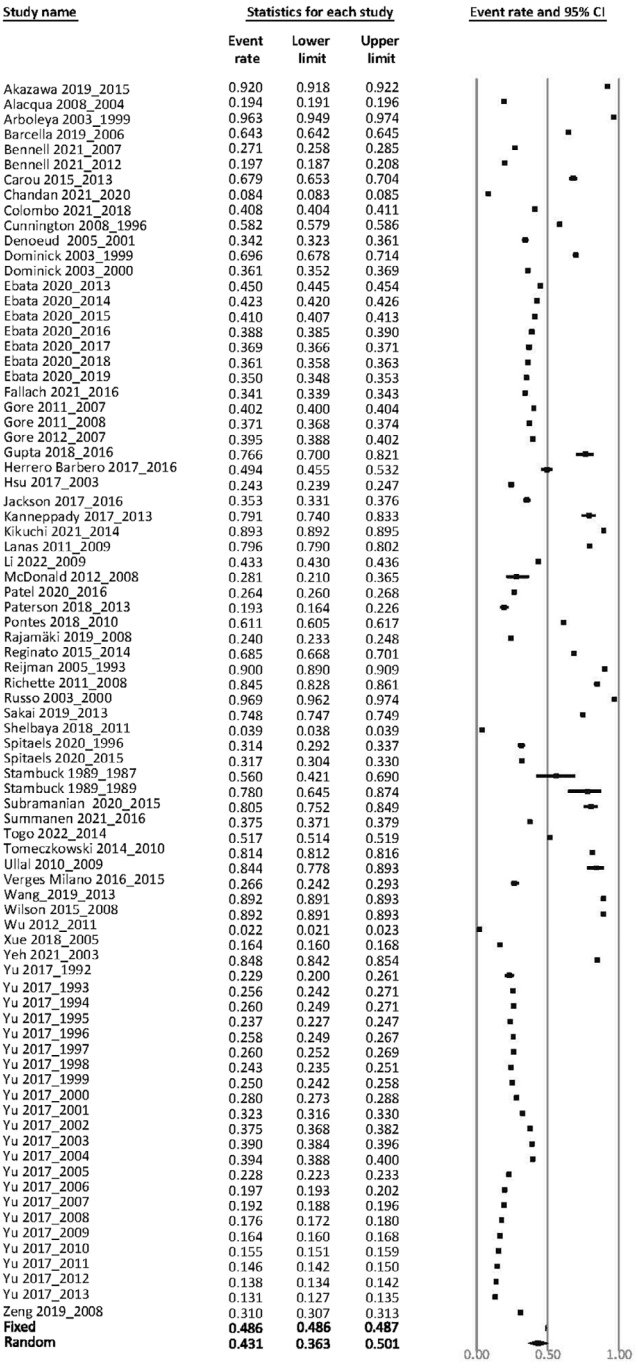

Figure 2. Proportion of participants with osteoarthritis prescribed a nonsteroidal antiinflammatory drug. The study name reports the name of the first author and publication year, followed by the associated data year.

analyses results are summarized in Table 3 and the forest plot shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

Prescribing estimates across country income status. Based on WHO income status, the pooled estimate of NSAIDs prescribing in high-income countries was 40.3% (95% CI 33.6, 47.4; n = 46 studies, I^2 = 8.5%, moderate quality of evidence) (11,12,25–36,38–43,45,46,48,50–56,58–64,65–73), greater in middle-income, including, respectively, lower-middle and upper-middle income countries, 83.4% (95% CI 74.8, 89.4; n = 4 studies, I^2 = 0%, moderate quality of evidence) (37,47,49,57) and 68.5% (95% CI 66.8, 70.1; n = 1 study, I^2 = 0%, high quality of evidence) (44). There were no studies from low-income countries. The stratified analyses results are summarized in Table 3 and the forest plot shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

The proportion of participants using different types of NSAIDs and dose. Fourteen studies (12,27,28,30,37,42,46,48,52,57,59,61,68,71) reported specific types of NSAIDs prescribed. A summary of the types of NSAIDs reported is shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157. Individual NSAIDs reported included aceclofenac, celecoxib, dexibuprofen, dexketoprofen, diclofenac, etodolac, etoricoxib, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, lornoxicam, meloxicam, nabumetone, naproxen, nimesulide, oxaprozin, piroxicam, rofecoxib, and tenoxicam. The most frequently reported prescribed NSAIDs in our sample was diclofenac, ibuprofen, and naproxen. High heterogeneity prevented pooling. Four studies (26–28,67) reported dosages. A summary of reported doses is detailed in Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

The proportion of participants using nonselective and COX-2 selective NSAIDs. Twenty-five studies provided data on the types of NSAIDs prescribed to patients with osteoarthritis. The pooled estimate of COX-2 selective NSAIDs was 11.0% (95% CI 8.0, 14.8; n = 23 studies, I^2 = 51.8%, moderate quality of evidence) (11,12,27,28,30,31,34–38,46,52,57,59,62,61,65–68,71,73) compared to nonselective NSAIDs at 34.5% (95% CI 27.0, 42.8; n = 23 studies, I^2 = 48.8%, moderate quality of evidence) (12,27,28,30,31,34,36–38,46,48,52,57,59,61,62,63,65–68,71,73). The stratified analyses results are summarized in Table 3 and the forest plot shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157.

Prescribing estimates per mode of delivery and mode of action. Ten studies (25,28,33,39,40,42,45,49,50,66) provided data on how NSAIDs were delivered. A summary is shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25157, grouping NSAIDs as either oral, topical, transdermal patch, or suppository, and grouping them as systemic and topical. High heterogeneity prevented pooling.

DISCUSSION

Our review established that 4 in every 10 participants diagnosed with osteoarthritis seeking health care were

Table 3. Summary of estimates from subgroup analyses*

	Studies, no.	I^2 value, %	Event rate (95%CI)
Osteoarthritis site			
Hip	3	0	0.349 (0.238, 0.479)
Knee	11	28.8	0.463 (0.369, 0.559)
Spine	1	0	0.669 (0.666, 0.672)
WHO regions			
East Asia and Pacific	10	31.7	0.468 (0.350, 0.589)
Europe and Central Asia	23	12.2	0.402 (0.318, 0.493)
Latin America and Caribbean	1	0	0.685 (0.668, 0.701)
Middle East and North Africa	1	0	0.341 (0.339, 0.343)
North America	12	11.0	0.326 (0.169, 0.536)
South Asia	4	3.0	0.834 (0.748, 0.894)
Income status			
High income	46	8.5	0.403 (0.336, 0.474)
Lower to middle income	4	0	0.834 (0.748, 0.894)
Upper to middle income	1	0	0.685 (0.668, 0.701)
NSAID type†			
Aceclofenac	6	–	0.143 (0.044, 0.376)
Celecoxib	7	–	0.033 (0.019, 0.055)
Dexibuprofen	1	–	0.000 (0.000, 0.000)
Dexketoprofen	2	–	0.055 (0.004, 0.470)
Diclofenac	13	–	0.133 (0.080, 0.213)
Etodolac	1	–	0.121 (0.086, 0.167)
Etoricoxib	5	–	0.023 (0.006, 0.078)
Flurbiprofen	1	–	0.001 (0.001, 0.001)
Ibuprofen	10	–	0.106 (0.046, 0.226)
Indomethacin	2	–	0.009 (0.005, 0.015)
Ketoprofem	1	–	0.042 (0.041, 0.043)
Ketorolac	1	–	0.010 (0.005, 0.020)
Lornoxicam	2	–	0.041 (0.003, 0.392)
Meloxicam	4	–	0.041 (0.006, 0.227)
Nabumetone	1	–	0.072 (0.068, 0.077)
Naproxen	10	–	0.047 (0.027, 0.078)
Nimesulide	1	–	0.111 (0.109, 0.112)
Oxaprozin	1	–	0.043 (0.040, 0.047)
Piroxicam	5	–	0.022 (0.010, 0.050)
Rofecoxib	3	–	0.022 (0.012, 0.042)
Rofecoxib/etoricoxib/valdecoxib	1	–	0.176 (0.128, 0.237)
Tenoxicam	1	–	0.003 (0.003, 0.003)
Selective versus nonselective			
Selective	23	51.8	0.110 (0.080, 0.148)
Nonselective to selective	23	48.8	0.345 (0.270, 0.428)
Delivery mode†			
Oral	10	–	0.387 (0.233, 0.568)
Patch	1	–	0.068 (0.066, 0.069)
Suppository	1	–	0.002 (0.002, 0.002)
Topical	1	–	0.212 (0.118, 0.350)
Mode of action†			
Systemic	10	–	0.400 (0.253, 0.568)
Topical	4	–	0.212 (0.118, 0.350)

* 95% CI = 95% confidence interval; NSAID = nonsteroidal antiinflammatory drug; WHO = World Health Organization.
† High heterogeneity present, except when 1 study was present.

prescribed a type of NSAID over 30 years. Prescribing was greater in middle-income countries, but there was no evidence available from low-income countries. NSAID prescribing was influenced by geographic region, and there has been a decrease in prescribing over time. Half of the included studies reported details on the types of NSAIDs prescribed, in which prescribing of nonselective NSAIDs was more prevalent than selective NSAID prescribing. Data were limited on prescribing for spine-related osteoarthritis, but NSAID prescribing was prevalent in approximately one-third of participants with hip-related osteoarthritis and nearly half in those with knee osteoarthritis.

Our review with a large sample is the first to examine the extent of NSAID prescribing for the clinical management of osteoarthritis and the potential factors associated with prescribing. Our thorough and sensitive search was conducted without

restrictions and used backward and forward reference and author citation tracking. The limitations of this study include some reporting bias, as most studies did not use a validated measurement instrument, and the use of observational studies, which is unavoidable in prevalence-based studies. We acknowledge that osteoarthritis can affect any joint, and clinical management can vary, and we conducted meta-regression to explore factors associated with NSAID prescribing, However, other factors than what we were able to include in the analysis, such as patient-related factors, were unlikely to contribute to prescribing, as only 42% of the variance was explained with the included study-related factors. We noted that data were limited on prescribing for spine-related osteoarthritis and on specific dosing regimens (regular or "when needed" use patterns), dose form, and duration. Our estimates are likely be an underestimate of actual NSAID prescribing, as some NSAIDs are available over-the-counter and do not always need a prescription. Only 1 study (39) reported the inclusion of NSAIDs prescribed as over-the-counter, and there was no difference in the estimates from clinical records of prescribing versus dispensing claims records. Our estimates could also be an underestimate. Our post hoc sensitivity analysis explored meta-analysis robustness, as there can be variance from studies contributing proportional data when close to 0 and 1. The analysis revealed higher pooled estimates.

The prevalence of NSAID prescribing to participants in primary and tertiary care with osteoarthritis was greater than in many reports of NSAID prescribing in the general population (74,75), for example, 16% in 2015 in the US (76), 22% in tertiary care in Nigeria (77), and 36% in Malaysian primary care (78). Half of the studies included in this review were from Europe. Included European studies as well as studies from high-income countries saw a rate of NSAID prescribing for osteoarthritis similar to what the literature indicates, as the general NSAID prescribing rate in the general population is lower than 40% (74,75,79). NSAID prescribing can differ between countries but also between populations, such as in older populations, where NSAID prescribing has been reported to be as high as 55% (80). Geographic differences of NSAID prescribing may be related to variance in the under- or overuse of medicines and variances in medical systems between different countries, including differences in reimbursement policies, national education campaigns for clinicians to promote the judicious use of NSAIDs (81,82) and marketing practices (83).

The majority of included studies were from high-income countries. Previous studies (84,85) determining prescribing patterns and use of NSAIDs in the general population have observed similar findings. The number of studies of prescribing patterns from middle-income countries continues to be limited. The few studies from middle-income countries suggested that NSAID prescribing is greater than in high-income countries. There could be several reasons to explain these differences, such as the availability and low cost of NSAIDs, and a greater number of NSAIDs may require prescription rather than being available over-the-counter compared to high-income countries. However, the extent of NSAID prescribing for osteoarthritis in low-income countries, and whether this prescribing has changed over time, is uncertain. The decrease in NSAID prescribing noted over time in our review coincides with the increase in opioid prescribing (84) for chronic noncancer pain over the last 2 decades, although recent opioid mitigation strategies following rises in opioid-related harms have begun to take effect. Previous studies have found that NSAID prescribing in the general population from high-income countries has also decreased over time (83,86,87).

The focus of this review was to determine NSAID prescribing among patients diagnosed with osteoarthritis. Therefore, we are still unclear about the prevalence of NSAID prescribing and use among people who self-reported nonclinically diagnosed osteoarthritis. We noticed that most studies (85%) did not require radiographic evidence for confirmation of osteoarthritis in their inclusion criteria. The use of NSAIDs may be higher than our pooled estimates and future research could explore differences between NSAIDs use and prescribing rates to understand adherence to clinical recommendations. Understanding the differences between NSAID prescribing and utilization can identify scenarios where overprescribing occurs.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mathieson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mathieson, Kobayashi, Abdel Shaheed, Simic, Machado, McLachlan.

Acquisition of data. Yang, Mathieson, Kobayashi, Abdel Shaheed, Nogueira, Simic, Machado, McLachlan.

Analysis and interpretation of data. Yang, Mathieson, Kobayashi, Abdel Shaheed, Nogueira, Simic, Machado, McLachlan.

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