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Terminologies and definitions used to classify patients with osteoarthritis: a scoping review

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Abstract

Objectives Osteoarthritis (OA), a prevalent and disabling condition, significantly burdens individuals and healthcare systems worldwide. It is characterized by joint pain, stiffness, and structural changes in cartilage, bone, and synovium. The clinical manifestations of OA vary widely, reflecting complex interactions among genetic, metabolic, biomechanical, and environmental factors. Despite progress in identifying OA clinical phenotypes, inconsistent terminology, including "phenotypes," "subtypes," and "subgroups," hinders effective communication and research translation. This review aims to synthesize existing literature on clinical OA phenotypes, terminology, and definitions and propose a research agenda.

Method This scoping review followed PRISMA-ScR guidelines, focusing on publications from 2010 to 2023 investigating clinical phenotypes in adult OA patients. Searches were conducted in MEDLINE, SCOPUS, and EBSCOhost using combinations of terms related to clinical phenotypes in OA. Studies were screened, duplicates removed, and relevant data were charted and analyzed by two independent reviewers.

Results From 196 identified studies, 50 were included in the final analysis. Eight clinical phenotypes were categorized, including inflammatory, biomechanical, metabolic, and pain-sensitization. minimal joint disease, psychologically driven, menopause, severe radiographic. Most studies focused on knee OA, with limited exploration of hand, midfoot, and hip OA. Phenotype-based management strategies demonstrated potential for improving treatment outcomes and guiding research.

Conclusion Standardizing terminology and leveraging phenotype-based frameworks hold promise for advancing personalized OA care and research. Future efforts should focus on validating criteria, developing accessible diagnostic tools, and addressing understudied OA phenotypes. This work highlights the value of tailoring interventions to specific OA phenotypes for improved patient outcomes.

Clinical trial number Not applicable

Keywords Osteoarthritis, Clinical, Phenotype, Patients

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Background

Osteoarthritis (OA) is the most common form of arthritis, affecting millions of people worldwide. It is a growing global burden related to the direct costs of treatment with limited effectiveness and the long-term societal impact. The disease is characterized by biochemical and morphological changes in articular cartilage, including fissuration, progressive cartilage loss, and focal matrix mineralization, bone changes such as osteophytes, subchondral cysts, subchondral sclerosis, and several changes in the synovial membrane, including secondary inflammatory processes [1, 2]. Although OA can affect any joint, the disease most commonly affects joints in the hands, feet, knees, hips, and cervical and lumbar spine. The disease is typically characterized by joint pain and stiffness, while clinical manifestations can vary significantly among individuals, reflecting a complex interaction between genetic, metabolic, biomechanical, and environmental factors [3].

The word phenotype commonly refers to the observable expression of an individual's genotype. While the individual's unique genetic composition characterizes genotypes, phenotypes are most readily observed as appearance, signs, and symptoms related to a particular disease [2]. A phenotype results from the interaction between their genotype and their environment. However, the connection between them is not clear-cut, and proteins, cells, and activated biological pathways differ between individuals. Clinical phenotypes in OA are identified and defined based on symptoms, physical examination findings, and imaging features [4]. These clinical phenotypes are essential because they help health professionals and researchers to better categorize patients into more homogeneous groups, which can influence treatment decisions and prognostic assessments. For example, phenotypes such as the inflammatory phenotype, characterized by signs of inflammation including swelling, heat, redness, and pain of the affected joints, and the metabolic phenotype, associated with obesity and metabolic disorders, have been identified [5]. However, these clinical phenotypes are not precisely defined, and there may be overlapping phenotypes and heterogeneity between patients with the same phenotype. Recognizing and understanding the clinical phenotypes of OA is crucial for several reasons. First, it would facilitate a more personalized approach to treatment. Given the heterogeneity of OA, a one-size-fits-all treatment approach is often ineffective while tailoring treatments to the individual's disease characteristics and mechanisms by identifying specific clinical phenotypes, potentially improving outcomes. Second, understanding clinical phenotypes can facilitate the development of new therapeutic targets. By distinguishing the pathways and mechanisms that drive different OA phenotypes, researchers can identify novel targets for drug development [6].

Third, the identification of clinical phenotypes has important implications for research. It could enable more precise patient selection for clinical trials, reducing variability in study outcomes and increasing the likelihood of detecting the effects of interventions. This precision can accelerate the pace of OA research and the development of new effective therapies [7].

Recognizing clinical phenotypes in OA represents a considerable advancement in understanding and managing OA. It underscores the importance of a personalized medicine approach, considering the unique characteristics of each patient's disease. As research continues to unravel the complexities of OA and its phenotypes, the prospects for more targeted and effective interventions improve, offering hope for individuals suffering from this debilitating condition.

Finally, various terminology is used in the literature to define a subset of patients, such as phenotype, subtype, or subgroups. This heterogeneity in terminology makes communication between researchers and healthcare professionals difficult. We need to standardize terminology to facilitate communication between stakeholders. For these reasons, a scoping review was conducted to map the research done in this area and to identify any existing gaps in knowledge [8].

The primary objective was to present a synthesis of the literature about clinical phenotypes based on commonly used stratification terminology. Secondary objectives were to describe the existing phenotype of patients with OA and define the research agenda to address the prioritized objectives.

Method

Protocol

The scoping review followed the regulations "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews " (PRISMA-ScR) and the recommendations of the Cochrane Collaboration [9].

Eligibility criteria

The criteria for being included in the current scoping review were papers published between 2010 and 2023, written in English, involving human participants over 18 years of age diagnosed with primary or secondary OA in any part of the body. They can include any system or method used to classify OA, such as radiographic classifications or clinical classification systems, but not molecular-based methods. The molecular-based patient classification was addressed in another paper drafted by WG3 COST action NetwOArk consortium. No geographic limitation was introduced. Quantitative, qualitative, and mixed-method studies were included to

consider different aspects of measuring treatment burden. Publications were excluded if using a term without defining or classifying it, sub-classifications of molecular phenotypes or endotypes, or analyses performed together with other musculoskeletal problems (i.e., rheumatoid arthritis, fibromyalgia, etc.). Including other musculoskeletal conditions could compromise the precision of the classification, as the features of those different conditions may overlap or mask the features specific to OA. This makes it difficult to isolate the characteristics specific to OA.

Information sources

To identify potentially relevant documents, the following bibliographic databases were searched from 2010 to 2023: The databases selected were MEDLINE, SCOPUS, and EBSCOhost, as they provide comprehensive coverage of peer-reviewed publications in the fields of rheumatology, musculoskeletal disorders, and clinical classification research. A specialist in a literature review (GGN) drafted the search strategies, which were further refined through expert consultation team discussions (European Cooperation in Science & Technology (COST - CA21110 - Building an open European Network on OsteoArthritis research (NetwOArk) working group dedicated to clinical phenotype). The final search strategy for MEDLINE, SCOPUS, and EBSCOhost can be found in supplementary file 1. The results were downloaded and imported into the Rayyan QCRI tool to help eliminate duplicates.

Search

The search words included Osteoarthritis OR OA and combination with the classification term clinical + (phenotype, subtype, subgroup), and the following keyword combinations. The keywords used in the search strategy were carefully selected based on terminology commonly employed in osteoarthritis literature, including variations related to clinical phenotypes, classification systems, and disease progression:

- "clinical phenotypes" AND (osteoarthritis OR OA).
- "clinical subtypes" AND (osteoarthritis[tiab] OR OA[tiab].
- "clinical subgroups" AND (osteoarthritis[tiab] OR OA[tiab])

This search did not include restrictions regarding the date or language. A secondary search analyzing the references in the articles obtained was also performed. Unpublished studies were not included. The last search was performed in November 2023.

Selection of sources of evidence

The selection of the studies was done by two researchers, both blinded, and any disagreements were discussed to come to a consensus. After selecting the publications from the databases, the duplicates were eliminated. After the elimination, titles, and abstracts of the selected papers were screened based on the inclusion and exclusion criteria by two reviewers working in pairs. The selected studies were then analyzed to assess compliance with the eligibility criteria. The information on the phases of the selection process was described through a PRISMA flow diagram (Fig. 1).

Data charting process and data items

A table was created that contained the data extracted from the included studies. The leading researcher (RK) extracted all relevant data from the studies, together with the rest of the authors such as: characteristics of the publication (author, title, country, year, study design), OA type and stage, number and sex of participants, diagnosis, terminology used [clinical phenotype, subtype, subgroup, other], and patients. Another researcher (GGN) then controlled to ensure the data was correct and independently assessed all articles, achieving a Cohen's kappa statistic of 0.85, indicating excellent inter-rater reliability and objective study selection. Any disagreements were resolved through discussion between the two reviewers or further adjudication by a third reviewer (AB). The other authors were involved in the design of the scoping review, data analysis, paper drafting, or reviewing and consensus. To better visualize the trends in terminology usage and the relationships between key concepts, two graphical representations were generated. A cumulative frequency graph was created to illustrate the temporal evolution of terminology mentions across the included studies. Additionally, a word cloud was constructed to highlight the most frequently used terms related to OA classification. These visualizations provide a clearer understanding of terminology trends and associations, complementing the quantitative data extracted from the studies.

Synthesis of results

The studies were grouped by the types of topics they investigated. They summarized the kind of settings, populations (OA and clinical phenotype), and study designs for each group, along with the measures used and main findings. The studies were grouped by their primary topic of investigation, defined by the localization of OA. Thereafter, subgroups of patients were formed based on OA patient characteristics and classified into eight categories according to symptoms, course, comorbidities, risk factors, imaging features, and pathophysiological mechanism: For the knee, there is minimal joint disease,

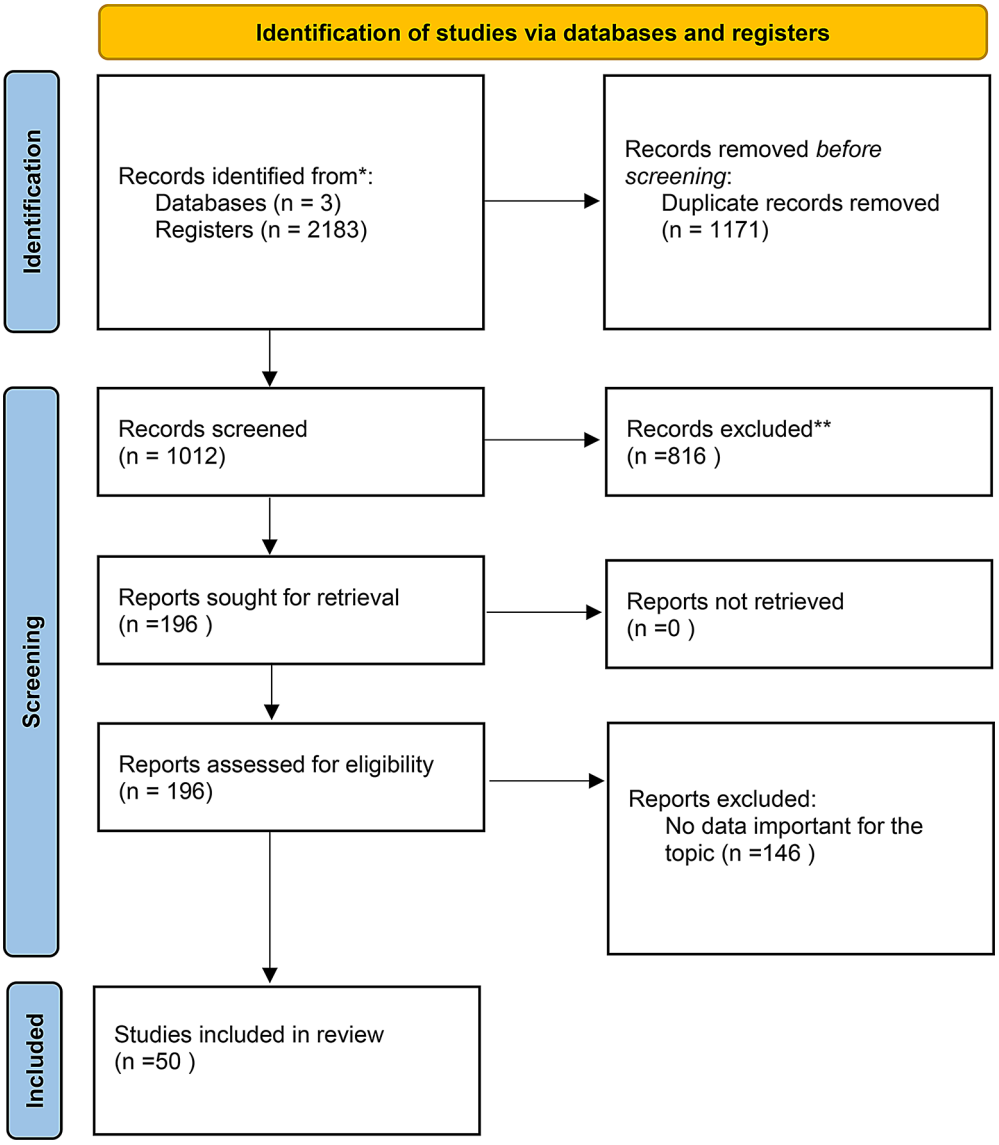

Fig. 1 Flow diagram PRISMA 2020. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

biomechanical, pain sensitivity and psychological factors, inflammation, metabolic influences, and menopause-driven and severe disease. The temporomandibular joint (TMJ), hand, hip, and midfoot OA were treated separately. This grouping facilitated the synthesis of results into distinct phenotype categories, ensuring a clear progression from the included studies to the phenotypes described. When a scoping review was identified, the number of studies included in the review that potentially met our inclusion criteria was counted, and how many studies had been missed by our search was noted (Fig. 1).

The data synthesis in this scoping review was conducted using a narrative synthesis approach. This method allowed us to integrate and summarize findings from diverse study designs and methodologies, focusing on patterns, relationships, and themes across the included literature.

Risk of bias in individual studies

To assess the risk of bias in individual studies, we employed the Newcastle-Ottawa Scale (NOS), a widely used tool for evaluating the methodological quality of observational studies. The NOS assesses three key domains: selection of study participants (max. 4 points), comparability of groups (max. 2 points), and outcome assessment (max. 3 points), with a total score of 9

indicating the highest methodological rigor. This tool was chosen for its robustness in appraising study design quality, risk of bias, and the reliability of reported outcomes, ensuring a systematic and objective evaluation of the included studies [10].

Results

Overview

The initial database search identified 196 studies, of which 50 were included in the final analysis after applying the inclusion and exclusion criteria. The studies encompassed various geographical locations, with the majority of them conducted in the USA and UK (Fig. 2).

Study characteristics

The study designs included in the review were primarily cohort studies (34.7%) and cross-sectional studies (28.6%), with the remainder comprising various other methodologies. The studies analyzed a wide range of clinical phenotypes and subtypes of OA, mainly focusing on knee OA and hand and midfoot OA, among others (Table 1).

The graph illustrates the evolution of research on osteoarthritis (OA) locations from 2011 to 2024. Knee OA consistently dominates the publications, peaking in 2015, 2021, and 2022. In contrast, studies on hip and hand OA remain limited, with a slight increase observed in recent years, while general OA (General OA that affects multiple joints in the body) research shows sporadic activity (Fig. 3).

The frequency distribution of OA by location shows knee OA being the most prevalent (78.4%). Other locations, such as hand and hip, account for significantly lower percentages (5.9% each), emphasizing the dominance of knee OA in clinical studies (Fig. 4).

The word cloud in Fig. 5 provides an overview of the most frequently co-occurring terms in the included studies. The prominence of terms such as phenotype, group, cluster, pain, OA, muscle strength, and knee highlights the key concepts associated with OA classification. The presence of terminology related to anatomical structures, symptomatology, and risk factors suggests that studies have primarily focused on clinical and biomechanical characteristics when defining OA phenotypes. This visualization helps to identify the central themes in the literature and their relative importance.

In addition, the cumulative frequency graph in Fig. 6 illustrates the evolution of terminology usage over time. The data reveal a steady increase in the use of the term phenotype, which has become the predominant classification term in recent years. In contrast, subtype has shown a moderate increase, whereas endotype and other terminology categories have remained relatively infrequent. These trends suggest a shift in the preferred nomenclature for classifying osteoarthritis (OA) subgroups in research, aligning with the broader focus observed in the word cloud.

Together, these visualizations provide a comprehensive perspective on terminology trends in OA research,

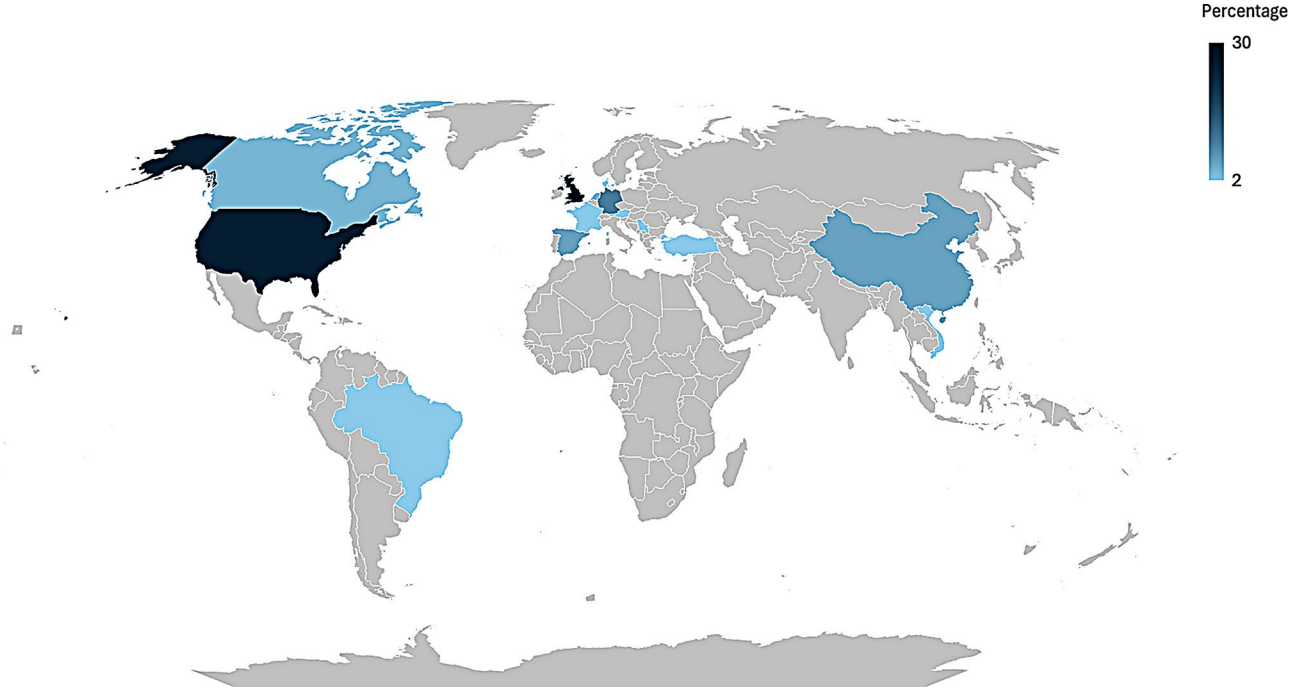

Fig. 2 Percentage papers by countries

Table 1 Frequency and distribution of clinical osteoarthritis locations

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Knoop J et al. [11]	2011	United States	Progression Subcohort	842	OsteoArthritis Initiative database.	63.2 ± 69.1	Knee	Minimal Joint Disease, Strong muscles, nonobese and weak muscle, obese and weak muscles and depressive	Phenotype
Castañeda S et al. [12]	2012	Spain	n/a	-	OA subchondral bone	-	General	(1) A new classification of primary OA, in which three subsets were postulated according to the predominant pathophysiological mechanism involved: genetic, menopause-related hormonal deprivation, and age. (2) Among these subsets, the estrogen deficiency-dependent OA subgroup is of special interest because subchondral bone (SB) may be a differentiated primary therapeutic target. 3. Another typical subgroup is the post-traumatic OA. 4. Subchondral osteoblast phenotype.	Subsets, subgroup, phenotype
Finan PH et al. [13]	2013	United States	Cross-sectional study	113	Patients with knee OA who met the American College of Rheumatology (ACR) criteria for knee OA	n/a	Knee	Compared Kellgren/Lawrence scale X-ray scores of knee arthritis with level of pain	Endophenotype marker of chronic pain
Hawker GA and Stanaitis I [14]	2014	England	Review	-	OA	n/a	General	OA on incidence and progression of other 'metabolic syndrome '-related conditions, especially cardiovascular disease and diabetes, and the impact of multimorbidity on the clinical management of OA.	OA phenotypes, subgroups
Thomas MJ et al. [15]	2015	England	Prospective observational cohort study	560 responders	Assessment Study of the Foot (CASF)	over 50 years	Midfoot	Females, adults over 75 years, and those in intermediate/routine occupational classes. Obesity, previous foot/ankle injury, and pain in other weight-loaded joints, but not high-heeled footwear or nodal interphalangeal joint OA, were associated with an increased risk of symptomatic midfoot	Phenotype and subtype.
Iijima H et al. [8]	2015	United States	Cross-sectional study	266	Japanese patients with medial knee OA	72.7 ± 6.94	Knee	Four phenotype based on static varus alignment and varus thrust were found to be partly associated with clinical outcomes in patients with medial compartment knee OA, showing that dynamic varus malalignment was associated with knee pain during gait (Range of motion, Gait velocity, Step length), and, combined with static varus alignment, was strongly associated with knee pain	Phenotype
van der Esch et al. [16]	2015	England	Cohort Design	551	Amsterdam OA (AMS-OA) cohort	61.7 (8.8)	Knee	minimal joint disease phenotype strong muscle strength phenotype, severe radiographic OA phenotype, obese phenotype, and depressive mood phenotype"	Phenotypes

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Jan Waarsing et al. [17]	2015	Netherlands	Cluster analysis	518	OA initiative	61 (±9) [45–79]	Knee	Four distinct clusters were identified with apparent differences in structural degradation and symptoms	Subtypes and clusters
Wesseling J et al. [18]	2015	Netherlands	Prospective cohort study (CHECK)	705	Early symptomatic knee OA aged 45–65 years with first onset knee pain or stiffness	56 (5.1)	Knee	3 groups of marginal, mild, and moderate pain trajectories/subgroups	Subgroups
Raynauld JP et al. [19]	2015	Canada	prospective study (secondary / post hoc analysis of baseline and 2-year data of a knee OA RCT)	143	Patients (40–80 years), with primary knee OA of the medial femorotibial compartment diagnosed according to the clinical and radiological criteria of the American College of Rheumatology,	-	knee	The concurrent presence of low VM area, high Vastus Medialis, % Fat, and high BMI identified a subgroup of patients with greater cartilage volume loss in the medial femur (P50.028) than the rest of the cohorte	Subgroup
Eymard F. et al. [20]	2015	France	Randomized, double-blind	559 patients older than 50 years	Caucasian ambulatory men and women aged 50 years with symptomatic and radiographic evidence of knee OA	62.8 [62.2–63.4] years	Knee	Type 2 diabetes predicted joint space reduction in men with established knee OA. No relationships were found between MetS or other metabolic factors and radiographic progression.	Subgroup
Dell'Isola A M [21]	2016	England	Digital Cohort Design	389	Hand osteoarthritis digital cohort	6.5 ± 7.4	Hand	The highly symptomatic cluster 5 was associated but not significantly with metabolic syndrome, and body mass index and C-reactive protein levels did not differ among clusters. Symptom intensity was significantly associated with joint destruction as well as with a physical and psychological burden	Phenotype and Subtyp".
Andrew Kittelson et al. [22, 23]	2016	United States	Latent class analysis	3494	OA initiative	65.2(± 8.5)	Knee	Four distinct pain phenotypes of knee OA were identified. Psychological factors, comorbidity status, joint sensitivity appear to be important in defining phenotypes of knee OA-related pain	Phenotypes of knee OA-related pain

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Cardoso JS et al. [23]	2016	United States	Cross-sectional study	292	Knee OA according to ACR criteria, obtained from 'the Understanding Pain and Limitations in Osteo-Arthritic Disease study'	57 (no measure of variation provided)	knee osteoarthritis	Clusters (PCA) based on pain sensitivity (1) low pain sensitivity to pressure pain (*N* = 39); (2) average pain sensitivity across most modalities (*N* = 88); (3) high temporal summation of punctate pain (*N* = 38); (4) high cold pain sensitivity (*N* = 80); and (5) high sensitivity to heat pain and temporal summation of heat pain (*N* = 41)	Phenotype
Frey-Law LA et al. [24]	2016	United States	Cross-sectional study (baseline data of a RCT (TANK)	346	People scheduled for TKR (advanced knee OA)	62.3 +/-9.6	Knee	Cluster analysis resulted in 5 pain sensitivity profiles: a "low-pressure pain" group, an "average pain" group, and 3 "high pain" sensitivity groups that were sensitive to different modalities (punctate, heat, and temporal summation)	Phenotype
Messier SP et al. [25]	2016	United States	Cross-sectional	136	Subsample from IDEA cohort; sedentary people with radiographic knee OA	64.0 +/- 5.6	Knee	No differences in lower extremity mechanics between the 'subgroups' of people with uni and bilateral knee OA	Subgroups
Deveza DJ et al. [26]	2017	England	Systematic Review	22,546	26 studies, 20 used a cross-sectional design, and 6 used a cohort design	50 to 73 years	Knee	Pain sensitization, psychological distress, radiographic severity, body mass index (BMI), muscle strength, inflammation, and comorbidities are associated with clinically distinct phenotypes. Gender, obesity, other metabolic abnormalities, the pattern of cartilage damage, and inflammation may be implicated in delineating distinct structural phenotypes.	Phenotype, Subtype", Subgroup
Herrero-Beaumont G et al. [27]	2017	Spain	Systematic Review	Not applicable	Not applicable	Not applicable	Knee	Biomechanical OA: mechanical with varus malalignment. physical activity and cartilage volume, overweight, osteoporotic, OA: The marked rise in the prevalence of OA in women around menopause and the presence of estrogen receptors. Metabolic OA: Metabolic factors, including high abdominal circumference, hypertension, high-fat consumption, and self-reported diabetes mellitus, were associated with early cartilage degradation measured.	Phenotype

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Dell'Isola A and Steultjens M [28]	2018	United States	Multi-center prospective longitudinal cohort study	599 patients	Osteoarthritis Initiative database.	63.6(45–79 years)	Knee	Minimal Joint Disease: Pain < 3 AND K&L < 2 at 24 months AND (Pain < 3 AND K&L < 2 at 48 months. Inflammatory phenotype: MOAKS score synovitis/effusion = 3 Metabolic disorders phenotype: Presence of diabetes AND BMI < 30, Presence of diabetes OR BMI < 30 and systolic pressure < 140 mmHg OR diastolic pressure < 100 mmHg. Chronic pain phenotype: CESD-*R* > 16 or al least 6 Tender points six located above and below the waist, on both sides of the body, and axially Malaligned biomechanical phenotype/ Valgus alignment < 2º and MOAKS lateral tibial condyle < 2.0 AND MOAKS medial tibial condyle < 1.0 OR Varus alignment < 2º AND MOAKS lateral tibial condyle < 1.0 AND MOAKS medial tibial condyle < 2.0) Bone and cartilage metabolism phenotype ((uNTXI, uCTXII, uCTX-1u, uCTX-1α > 75th percentile) OR (sComp, sHA > 75th percentile) (uNTXI, uCTXII, uCTX-1û, uCTX-1α > 65th percentile) OR (sComp, sHA > 65th percentile)	Phenotype and Subtype
Bay-Jensen AC et al. [29]	2018	Denmark	Review	n/a	n/a	n/a	n/a	inflammatory, trauma or mechanical, metabolic, cartilage or bone-driven phenotypes	Phenotype and subtype
Büchele G et al. [30]	2018	Germany	cohort study	809 patients (389 knee, 420 hip)	Patient with knee and hip osteoarthritis	65 (58–70)	65 (67 knee; 62 hip)	cardio-metabolic phenotypes	Phenotype
Mobasheri et al. [31]	2019	England	Review	n/a	n/a	n/a	Knee	Metabolic syndrome phenotype, Bone and cartilage metabolism phenotype, Mechanical overload phenotype, Minimal joint disease phenotype. Secondary phenotypes (Cristal disease, Traumatic injury-driven, Resolved previous auto-immune arthritis, Occupational injury); Age-related and systematic phenotypes (metabolic disease, Ageing and senescence-driven, Endocrine disease); Intraarticular phenotypes (articular cartilage, synovitis-driven inflammatory, Subchondral bone, Meniscal-associates); Extraarticular phenotypes (Ligament and tendon laxity, Sarcopenic, Varus and valgus mal-alignment)	endotype, phenotype

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Teixeira et al. [32]	2020	Germany	Exploratory Control	63	OA	60.6 (median)	Knee	Association of clinical variables with pain intensity perception with varying levels of Conditioned Pain Modulation response	n/a
Miles C and Greene A [33]	2020	England	Retrospective analysis	455	OA	62.2 (9.5)	Knee	Investigate the changes in spatial-temporal gait parameters and clinical measurements following treatment with a non-invasive foot-worn biomechanical device	n/a
Bennell KL et al. [34]	2020	England	Randomized control trial	128	OA	61.7	Knee	Compare the effectiveness of two exercise programs.	n/a
Munugoda et al. [35]	2020	Germany	Observational study	1046 older adults	Australian Orthopaedic Association National Joint Replacement Registry	50–80 year	Knee	Obesity of the high high-risk	subgroups
Kittelson AJ et al. [36]	2021	England	Original article, prospectively designed cross-sectional study	183 people (152 pts. and 31 HSs)	152 people (96 woman) with knee OA (64,5% woman) and from 31 pain-free individuals (64,5% woman)	50–85 (age of patients 65.2+–8.5; age of healthy subjects 64.9+–9.0)	Knee	**Four phenotypes of knee OA** were identified using *psychological factors*, *comorbidity status*, *pain sensitivity, and leg strength*. Group 1 (9% of the study population) had **higher FCI** (Functional Comorbidity Index) scores. Group 2 (63%) had elevated **pain sensitivity and quadriceps weakness** relative to group 4 and healthy older adults. Group 3 (11%) had **higher PCS** (Pain Catastrophizing Scale) scores than all other groups. Group 4 (17%) had **greater leg strength**, except relative to healthy older adults, and reduced pain sensitivity relative to all groups.	"subgroups (also known as phenotypes)"
Xu T et al. [37]	2021	China	case-control	OA (40) / RA (40) / Controls without pain (40)	OA, RA, Healthy	57.22 (16.64)	General	Comparison between objective and subjective reports on physical activity/sleep in the three patient groups.	Arthritis subtype
Knoop J et al. [38]	2021	England	trial cohorts and one cross-sectional cohort	1211	OA	63.6	Knee	stratification algorithm (regarding musculature or exercise)	n/a
Güzel B et al. B [39]	2021	Turkey	Observational study	100	OA	62 (6)	Knee	Associations between radiographic phenotypes and the presence of metabolic syndrome in OA	Phenotype
Guehring H PG et al. [40]	2021	United States	Randomzed control trial	549	OA (SAR / non-SAR)	65 (median)	Knee	Pain outcomes and cartilage thickness change in a subgroup at risk (SAR) of further progression of knee osteoarthritis and treatment with sprifermin	n/a
Fawole HO et al. [41]	2021	England	Multicenter Study	484	OA	55–84 (range)	Knee	Physical activity associated with fatigue, and quantify the extent of potential mediation through depressive symptoms or physical function on OA	n/a

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Zhu Z a Hu G and Jin F and Yao X [42]	2021	England	series of surveys	1510 (arthritis), 9584 (non-arthritis)	OA, other arthritis (mixed), non-OA	42.8	General	Lumbar BMD was associated with OA but not with RA	n/a
Nishigami T et al. [43]	2021	England	Cohort	303	OA	69.1 (9.9)	Knee	Existence of subgroups based on data from multiple pain-related variables	Phenotype
Duarte-Salazar C et al. [44]	2022	Spain	cross-sectional study	119	Patients with osteoarthritis of the hand.	65.6 ± 8.3 and 59.9 ± 7.3 years	Hand osteoarthritis	These factors (pain, nodes, and radiographic changes) are associated in different magnitudes in individuals with erosive and non-erosive HOA, depending on the stage of the disease: either active (inflammatory flares) or chronic stage (structural abnormalities). Pain is an important determinant that substantially contributes to functional limitations in erosive and non-erosive HOA	Phenotype and subtype
Hess S MT et al. [45]	2022	Germany	cross-sectional study	2692 (OA), Non-OA (141)	OA, non-OA	71.1 (8.5)	Lower limbs	Alignment of OA knees and investigate whether femoral and tibial joint lines vary within patients with the same overall lower limb alignment.	Phenotype
Knoop J et al. [46]	2022	England	qualitative study	15	Patients with knee OA	NA	Knee OA	'High muscle strength subgroup''Low muscle strength subgroup''Obesity subgroup'	Phenotype, subgroup
Nelson AE et al. [47]	2022	United States	prospective cohort study	3330	Patients with knee OA	61.4 ± 9.1	Knee OA	We identified six biclusters (groups of features and knees) within the baseline OAI data with varying prognoses. Biclusters may represent potential KOA phenotypes (e.g., progressor phenotype(s)) within the larger cohort. Novel application of existing methodologies can provide insights into OA phenotypes and the development or progression of disease. Additionally, identifying phenotypes with differing prognostic associations may identify groups that are most likely to respond to specific interventions.	Phenotype, ubgroup
Hangaard S, Boesen M and Bliddal H and Wirth W [48]	2022	Germany	Follow-up	108	OA	63 (9.3)	Knee	Radiographic knee OA grading with Ahlbäck scores & KLG for prediction of cartilage thickness loss over 1 year	n/a
Pihl K et al. [49]	2022	United States	Observational study	73.072	OA	65.3	Knee and/or hip	Prognostic factors of change in health outcomes following an 8-week exercise therapy	n/a

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Stamenkovic et al. [50]	2022	Serbia	Retrospective cohort study	21,740 (7018 had osteoarthritis of peripheral joints and spine)	Patients with the presence of clinical, radiological, and laboratory OA parameters	63.107 ± 8.300	Knee, hip, spine, peripheral joints	osteoporosis	Subgroup
Cao TN et al. [51]	2022	Vietnam	Cross-sectional study	257 (195) in the knee osteoarthritis group and 62 in the nonknee osteoarthritis group)	Older patients with asymptomatic hyperuricemia	73.31 ± 7.96	Knee	Patient with asymptomatic hyperuricemia	Subgroup
Binvignat et al. [52]	2023	United States	Cohort Design	389	Digital Cohort Design (DIGICOD)	66.5 ± 7.4 years	Hand	Pain score was > 41 out of 100 in one-third of patients, Association of symptom intensity, joint destruction, and sex. Aesthetic discomfort was associated with erosive HOA and nodes. The highly symptomatic cluster was associated with metabolic syndrome. Function impairment was associated with thumb base pain. Symptom intensity was related to physical and psychological burden. Patients' overall main expectation was physical function	Phenotype

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Copp G, Robb KP and Viswanathan S [53]	2023	China	Review	610 treated pts.	356 patients (59%) were female, and 231 (38%) were male, while sex was not specified for 22 patients (3%).	between 50 and 60 years	Knee	Two-step cluster analyses were performed to classify the patients, using hip flexion, extension, abduction, and external/internal rotation muscle strength (cluster analysis 1); relative hip muscle strength to total hip strength (i.e., hip muscle strength balance; cluster analysis 2); and both hip muscle strength and muscle strength balance (cluster analysis 3) as variables. The association between the phenotype and hip OA progression over 12 months (indicated by joint space width (JSW) > 0.5 mm) was investigated. RESULTS: Radiographic progression of hip OA was observed in 42% of the patients. The patients were classified into 2 phenotypes in the 3 cluster analyses. The solution in cluster analyses 1 and 3 was similar, and **high-function** and **low-function phenotypes** were identified; however, no association was found between the phenotypes and hip OA progression. The phenotype 2 – 1 (high-risk phenotype) extracted in cluster analysis 2, which had relative muscle weakness in hip flexion and internal rotation, was associated with subsequent hip OA progression, even after adjusting for age and minimum JSW at baseline (adjusted odds ratio [95% confidence interval], 3.60 [1.07–12.05]; *P* =.039). The phenotype based on hip muscle strength balance, rather than hip muscle strength, may be associated with hip OA progression.	Phenotype
Jansen Nej Sma et al. [54]	2023	England	An ongoing prospective cohort study (sub-study of the third sub-cohort of the Rotterdam Study (RS-III)	682	women with **knee OA in MRI** sub-study for investigation of **early signs of knee OA**, where additional knee-specific baseline and 5-year follow-up measurements	53.33	Knee	**Cartilage defects**, **osteophytes**, **BMLs**, **effusion-synovitis**, **and Hoffa-synovitis** were reported. A cartilage score of 1 was considered as having cartilage defects. Osteophytes and BMLs were indicated present when grade (1) Effusion-synovitis and Hoffa-synovitis were indicated present when grade (2) The presence of a horizontal, vertical, complex, or root tear was considered as having a meniscal tear. *Participants with MetS had a higher BMI, were more often diabetic, were lower educated, and had a lower physical activity pattern compared to participants without MetS.***A higher z-MetS was associated with the presence of osteophytes** in the medial and lateral TF compartment and with the **presence of effusion-synovitis**. A higher z-MetS score was associated with the presence of PF and medial and lateral TF OA.	Clinical phenotype

Table 1 (continued)

Authors	Year	Country	Design	Sample size	Type population	Age (SD)	Location OA	Clinical phenotype	Terminology used (endotype, phenotype, subtype, other)
Demanse et al. [55]	2023	United States	A multi-center, longitudinal (2004–2016), prospective observational cohort study	4796	Both sexes • **Progression-cohort** ($n = 1390$, 29%): frequent knee symptoms and radiographic signs of tibio-femoral KOA.	45–79	Knee	Deep embedded clustering (**DEC**) and multiple factor analysis with clustering (**MFAC**) approach. DEC resulted in **5** and MFAC in **3** distinct patient phenotypes. Both identified a **"comorbid" cluster** with higher body mass index (BMI), relevant comorbidity burden, and low levels of physical activity. Both methods also identified a **younger and physically more active cluster** and an **elderly cluster with functional limitations** but low disease impact. The additional two clusters identified with DEC were subgroups of the **young/physically active** and the **elderly/physically inactive clusters**.	Clinical phenotype
Ji-Ling Feng et al. [56]	2023	China	Retrospective study	109	TMJ OA	36 (10)	TMJ	Three distinct groups of bone changes characterized by volume and thickness decrease	Groups and Subgroups
Felipe Gonzalez et al. [57]	2023	Brazil	Cross-sectional study	42	advanced OA	NA	Knee	Body mass index (BMI) was the only variable associated with a specific gait profile	Profile
Kalpana Sharma et al. [58]	2023	Austria	Cross-sectional study	600	FNHI-OAI biomarker	61 (9)	Knee	Medial meniscal extrusion was consistently positively associated with combined radiographic/symptomatic progression	Subgroups
Harvi Hart et al. [59]	2024	Canada	Cross-sectional study	48	Patello Femoral	NA	Knee	Distinct sex-based differences in gait characteristics	Subgroups

Summary Table OA: Osteoarthritis; ACR: American College of Rheumatology; PCA: Principal Component Analysis K&L: Kellgren and Lawrence; CESD-R: Center for Epidemiologic Studies Depression Scale-Revised; MOAKS: MRI Osteoarthritis Knee Scor; uNTXI: Urinary N-terminal telopeptide of type I collagen; uCTXII: Urinary C-terminal telopeptide of type II collagen; uCTX: Urinary C-terminal telopeptide; BMD: Bone Mineral Density; OAI: Osteoarthritis Initiative; KLG: Kellgren-Lawrence Grade; MetS: Metabolic Syndrome; BMLs: Bone Marrow Lesions

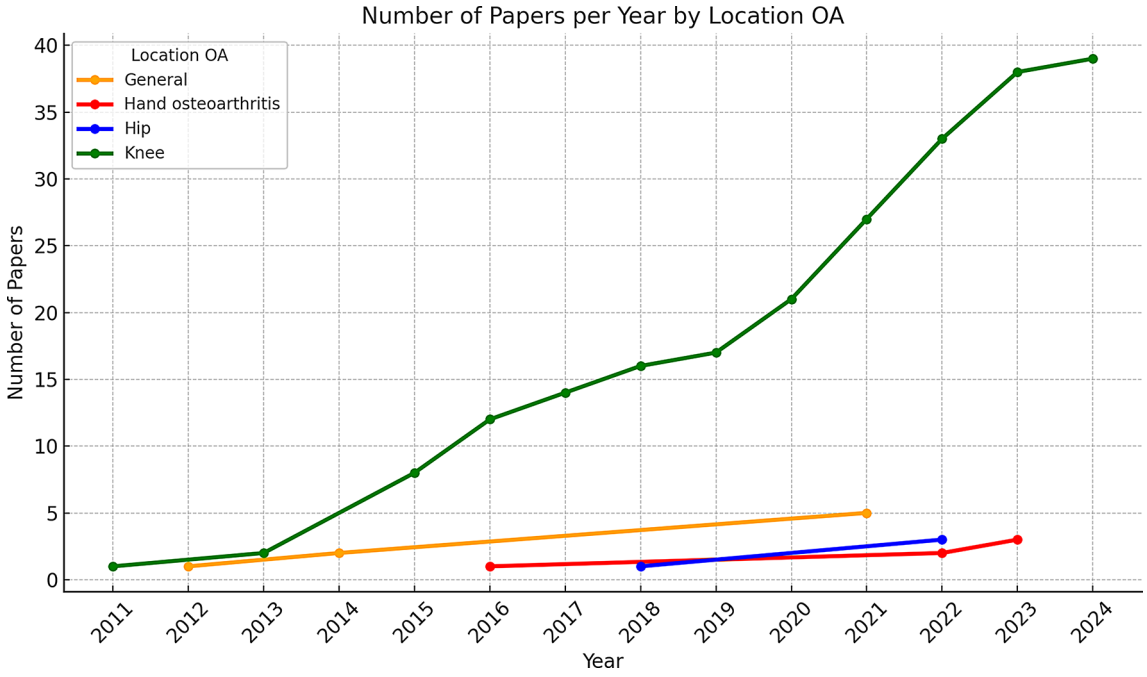

Fig. 3 Cumulative numbers of papers on osteoarthritis by location from the years 2011 to 2024

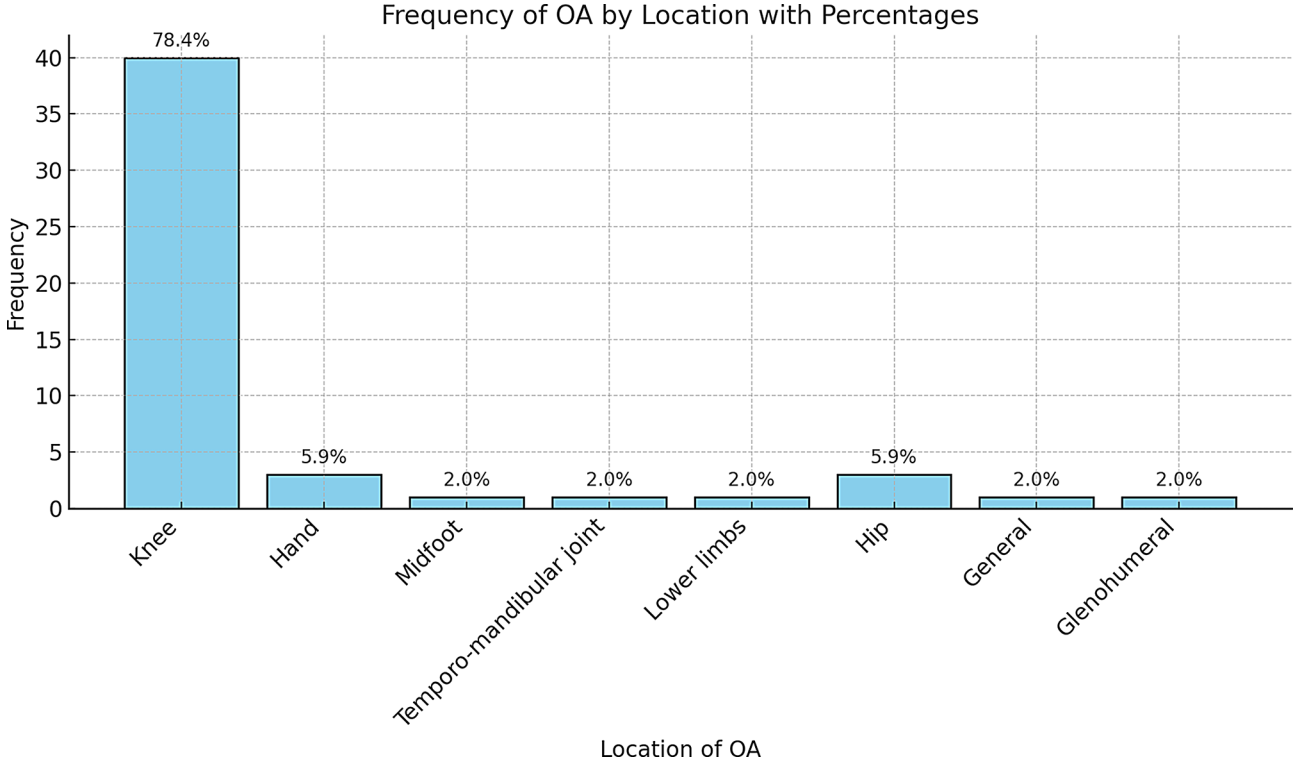

Fig. 4 Distribution of frequency and percentage of osteoarthritis by location

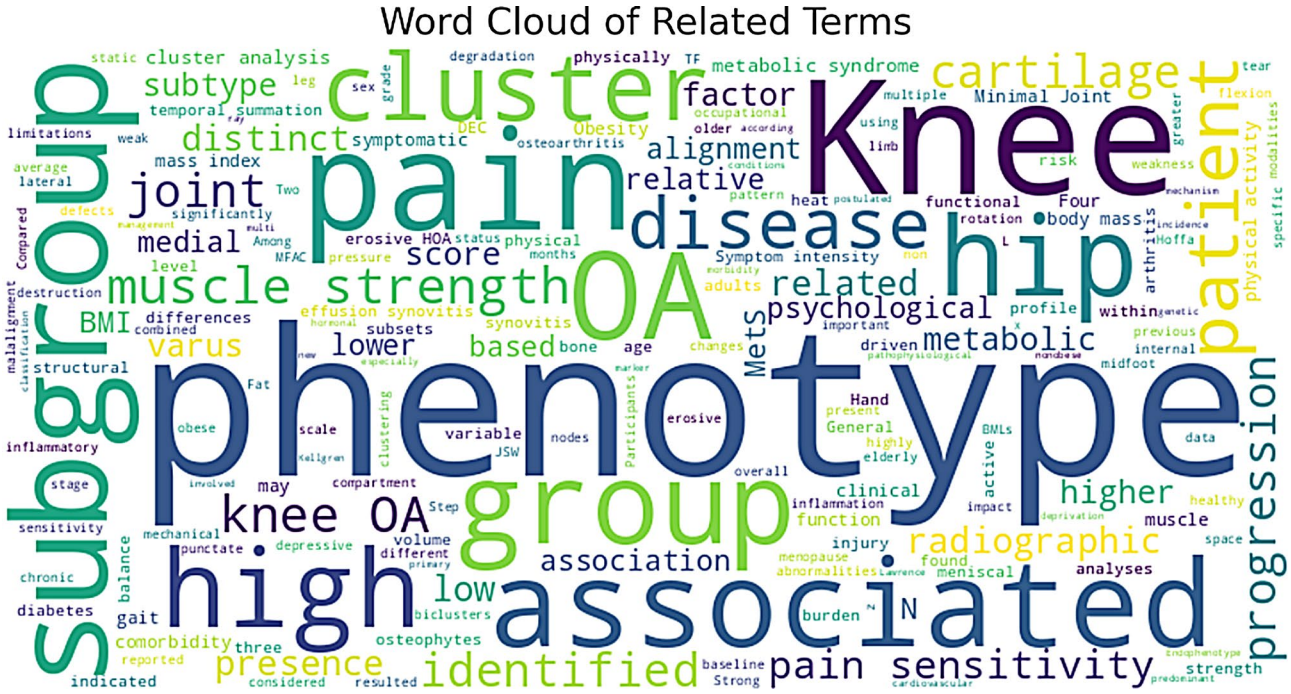

Fig. 5 Word could have related terms

Fig. 6 Cumulative evolution of terminology metions

complementing the quantitative findings extracted from the studies.

Clinical phenotypes described in knee OA (Fig. 7)

Minimal joint disease phenotype [11, 28, 47, 48, 50]

Description: This phenotype is characterized by minimal clinical symptoms, including low levels of pain (Pain intensity < 3 on a VAS scale) and minimal radiographic evidence of knee OA (Kellgren & Lawrence grade I or II at 24 months).

Implications: Patients with this phenotype may not require invasive interventions but should be monitored for disease progression. Lifestyle modifications and physical therapy are sufficient to manage their condition initially [28].

Pain sensitization and psychologically driven phenotype [13, 18, 22–24, 26, 28, 32, 36, 38, 40, 43, 46]

Description: This group experiences heightened pain sensitivity and psychological distress, which significantly affect their quality of life. Defined by chronic pain with a Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) score ≥ 16 or the presence of tender points above and below the waist on both sides of the body. And associated with high pain sensitivity, psychological distress, depressive symptoms, radiographic severity, BMI, loss of muscle strength, inflammation, and comorbidities [13, 26].

Implications: Management strategies should include comprehensive pain management approaches, including pharmacological pain treatments, physical therapy, and psychological support to address both the physical and emotional aspects of the disease. A multidisciplinary approach is recommended to improve patient outcomes [26].

Biomechanical OA phenotype [8, 16, 17, 27, 33, 34, 39, 41, 46, 55]

Description: this phenotype emphasizes the role of mechanical stress factors, such as varus or valgus

Fig. 7 Graphical summary of clinical phenotypes in osteoarthritis and their therapeutic implications

alignment (inward or outward angulation of the leg to the thigh), knee flexion dynamic varus or valgus during gait, overweight, professional or sports knee trauma, meniscus lesion professional mechanical factors, and loss of muscle performance in the development and progression of OA [16, 17].

Implications: Interventions may include weight management, physical therapy, physical activity, including exercise, orthotic supports, and, in some cases, surgical options to correct alignment and reduce mechanical stress on the knee joints [27].

Inflammatory phenotype [8, 20, 26, 28, 29, 31, 34]

Description: significant inflammation is characterized by a MOAKS score of synovitis/effusion = 3 [28], pain at rest, and pain intensity flare.

Clinical Implications: treatment may require anti-inflammatory medications and close monitoring of inflammatory markers. Interventions to reduce inflammation can help manage symptoms and slow disease progression [28].

Metabolic sensitization phenotype [14, 19, 20, 26, 31, 35, 51, 54, 57]

Description: associated with the presence of diabetes and a BMI > 30, or either condition combined with controlled blood pressure (systolic pressure < 140 mmHg or diastolic pressure < 100 mmHg).

Clinical Implications: Management strategies should focus on controlling metabolic conditions such as diabetes and hypertension. Weight management and lifestyle modifications are crucial for these patients [20].

Menopause-driven phenotype OA [12, 31, 59]

Description: It is noted for its prevalence in women around menopause and is associated with estrogen receptors [12].

Clinical Implications: Hormonal treatments may be considered in managing symptoms alongside standard OA treatments such as pain management and physical therapy [12].

Severe radiographic OA phenotype [13, 16, 17, 25, 28, 53, 58]

Description Characterized by severe radiographic changes in the knee joint, often accompanied by significant structural damage [17, 28].

Clinical implications Advanced imaging techniques and more aggressive treatments, such as injections or surgery, may be necessary for these patients [28].

Other osteoarthritis phenotypes

Clinical phenotypes in hand OA [21, 44, 52]

Description Characterized by a highly symptomatic cluster within a specific digital cohort, showcasing variability in symptom presentation in hand OA. Symptoms can range from minimal to severe, affecting daily activities and quality of life [20]. Erosive and non-erosive are the two main forms identified. The most Painful hand OA is associated with the erosive form.

Implications Treatment may include physical therapy, orthoses, and targeted interventions to manage pain and maintain hand function. The variability in symptoms necessitates personalized treatment plans [21].

Clinical phenotypes in midfoot OA [15]

Description This phenotype is more common among females, individuals over 75, and those with specific comorbidities. It indicates a distinct clinical presentation, possibly affecting mobility and balance [15, 60].

Implications Management strategies should focus on footwear modifications, pain management, and interventions that reduce, preserve, or improve mobility and reduce the risk of falls [27].

Clinical phenotypes in hip OA [7, 30, 49, 50]

- **Description**: Hip OA phenotypes often involve muscle imbalance and structural damage. Cluster analyses highlight phenotypes associated with hip muscle strength deficits, such as reduced hip flexion and internal rotation strength.
- **Implications**: Patients with muscle weakness phenotypes exhibit a higher risk of disease progression. Rehabilitation strategies should emphasize strength restoration and joint stabilization [7, 49].

Clinical phenotypes in temporomandibular joint (TMJ) OA [56]

- **Description**: TMJ OA presents distinct structural changes, including loss of bone volume and condylar thinning. Phenotypic groups exhibit varying degrees of morphological damage and functional limitations.
- **Implications**: Early diagnosis through advanced imaging (CBCT) can facilitate targeted therapies to mitigate joint deterioration and functional impairment [56].

Table 2 outlines a prioritized research agenda highlighting the necessary steps to advance the definition, validation, and implementation of clinical osteoarthritis

Table 2 Research agenda

• To identify the optimal clinical criteria or criteria cluster allowing diagnosis of OA phenotypes.
• To validate the criteria used to define clinical phenotypes
• To develop robust clinical and biochemical tools for the diagnosis of OA phenotypes
• To implement OA phenotypes diagnosis in clinical practice
• To identify comorbidities of different OA subgroups
• To develop a phenotype-based strategy for the management of OA
• To implement a clinical phenotype approach in OA treatment development.
• To evaluate the efficacy of existing and innovative OA treatments according to patient phenotype to increase their efficacy.
• To elaborate guidelines for the management of OA based on clinical phenotype recognition.

(OA) phenotypes. This framework is essential for guiding future research, improving patient stratification, and developing personalized treatment strategies based on clinical phenotype recognition.

Risk of bias

Following the application of the Newcastle-Ottawa Scale (NOS) to the reviewed articles, the majority of the studies demonstrated moderate to high methodological quality. Most studies received scores ranging from 7 to 9 out of a maximum of 9 points, indicating strong adherence to participant selection criteria, comparability, and outcome assessment.

- Selection (max. 4 points): Most studies scored 3 or 4, reflecting well-defined inclusion criteria and appropriate study designs.
- Comparability (max. 2 points): The majority achieved 2 points, indicating adequate control of confounding factors through statistical adjustments or study design.
- Outcome (max. 3 points): The distribution was balanced between 2 and 3 points, demonstrating that most studies employed valid methods for outcome assessment and ensured appropriate follow-up.

Overall, studies that obtained 9 points can be considered high-quality, making them highly reliable for drawing robust conclusions regarding clinical phenotypes and osteoarthritis progression. Studies scoring 7 points present some methodological limitations but remain valuable in the analysis of the topic.(supplementary file).

This assessment suggests that the evidence base used is strong and appropriate to support the review on terminologies and definitions in osteoarthritis classification. However, it would be advisable to incorporate more rigorous prospective studies with extended longitudinal follow-up to further enhance the validity of conclusions.

Discussion

This scoping review represents a significant step forward in categorizing OA patient subgroups by summarizing the terminology used in the literature. The predominant term identified, "phenotype," aligns with the definition as an observable characteristic resulting from gene expression [1, 2]. Our analysis of the current research area has allowed for the identification of seven proposed phenotypes in knee OA. These phenotypes include minimal joint disease, pain sensitization and psychologically driven, biomechanical, inflammatory, metabolic sensitization, menopause, severe radiographic [16, 21].

Delineating phenotypes has profound clinical implications, underscoring the necessity for phenotype-based management approaches. For instance, while both are influenced by weight, metabolic sensitization and biomechanical phenotypes require distinct therapeutic strategies. Weight loss is universally beneficial for overweight individuals, but additional interventions, such as physical therapy or surgical correction of malalignment, may be crucial for biomechanical phenotypes [17, 27]. In contrast, the metabolic sensitization phenotype requires weight loss, decreased fat tissue, increased lean mass, and control of diabetes and hypertension. Such differentiation in treatment highlights the limitations of a one-size-fits-all approach and emphasizes the value of tailoring interventions to the unique characteristics of each phenotype.

Another critical observation is the utility of these phenotypes in enhancing patient stratification for research and clinical trials. Homogeneous grouping of patients based on phenotype can reduce variability, leading to more robust outcomes and accelerating the development of targeted therapies [28]. Additionally, the potential role of artificial intelligence (AI) in clustering phenotypes by analyzing clinical, diagnostic, and imaging markers is promising. Incorporating AI-driven models could improve the precision of phenotype identification and facilitate their integration into routine clinical practice [31].

The identification of phenotypes also has implications for early diagnosis and preventive strategies. For example, the inflammatory phenotype can benefit from targeted anti-inflammatory treatments, potentially delaying disease progression and preserving joint function [8, 20]. Similarly, the metabolic phenotype emphasizes the importance of managing comorbid conditions, such as diabetes and hypertension, to mitigate their impact on OA symptoms and progression [21]. Early identification of the minimal joint disease phenotype, when symptoms are not a limiting factor for physical activity and rehabilitation, is a key challenge of OA prevention. These examples highlight the relevance of an early interdisciplinary approach to managing OA involving endocrinology, psychology, and rehabilitation specialists.

Rare phenotypes of osteoarthritis, such as those associated with Mendelian disorders (e.g., camptodactyly-arthropathy-coxa vara-pericarditis syndrome) and chondrodysplasias, highlight the influence of genetic factors in the development and progression of the disease. These conditions demonstrate that specific genetic mutations can disrupt cartilage and joint homeostasis, leading to early-onset osteoarthritis. Consequently, the inclusion of a 'genetically driven OA' phenotype is essential to capture the spectrum of osteoarthritis presentations influenced by hereditary factors. Recognizing these phenotypes not only enhances the classification framework but also underscores the need for targeted therapeutic strategies tailored to these unique genetic drivers.

Despite these advancements, challenges remain in refining the criteria used to define phenotypes. Future research should prioritize the identification of specific and sensitive clinical markers that differentiate phenotypes effectively. Furthermore, accessible and cost-effective diagnostic tools are critical for implementing phenotype-based management in clinical settings. These tools should focus on easily identifiable markers, such as clinical examination findings, biochemical markers and/or patient-reported outcomes, that can be directly linked to specific therapeutic protocols [26]. Cohort studies and longitudinal analyses will be indispensable in validating these markers.

The variability observed in hand and midfoot OA phenotypes suggests additional research is necessary to understand their unique characteristics and treatment requirements [15, 26, 60]. Unlike knee OA, these phenotypes are less frequently studied, representing an area of potential exploration for improving patient outcomes.

Meniscal injuries alter knee biomechanics by disrupting load distribution, increasing joint instability, and accelerating cartilage degeneration. This leads to abnormal tibiofemoral contact forces and contributes to osteoarthritis (OA) progression. Understanding these mechanical changes is essential for accurately defining OA phenotypes and their clinical implications.

This scoping review adopted a rigorous methodology guided by the PRISMA-ScR checklist, ensuring transparency and reproducibility in synthesizing the existing literature. It is the first scoping review to systematically examine clinical phenotypes in OA, thereby addressing a critical gap in the field. Including studies spanning 2010 to 2023 and focusing on diverse phenotypes across various OA subtypes provides a comprehensive overview. Nevertheless, some limitations must be acknowledged. First, excluding unpublished and ongoing research may have led to omitting relevant findings, particularly emerging data in this rapidly evolving field. Second, while our search strategy was robust, the reliance on English-language publications may have introduced a language bias. Lastly, the heterogeneity in defining and categorizing OA phenotypes among included studies highlights the need for standardization, which could influence the reproducibility of our findings. Despite these limitations, the review provides a valuable foundation for advancing phenotype-based approaches in OA research and clinical practice.

Conclusion

In conclusion, this scoping review overviews clinical classifications identified in the literature based on the most commonly used terminology. It describes the seven clinical knee phenotypes and a list of the associated signs and symptoms. We also suggest a list of future research questions that should allow us to better characterize the phenotypes in OA by developing robust clinical and biochemical diagnostic tools using cohort studies and longitudinal analyses.

Supplementary Information

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Supplementary Material 1

Author contributions

Conceptualization: All authors; Methodology: Gabriel Gijon-Nogueron (GGN), Yves Henrotin, and Rositsa Karalilova (RK); Formal analysis: Gabriel Gijon-Nogueron (GGN) and Yves Henrotin Data curation: Peter Balint(PB), Predrag Ostojic (PO), Marienke van Middelkoop (MvM), Rintje Agricola (RA), Josefine E. Naili (JN); Rositsa Karalilova (RK), Gabriel Gijon-Nogueron (GGN), Darko Milovanovic(DM), Stanislava Popova(SP) and Maria Kazakova (MK); Writing—original draft preparation: Gabriel Gijon-Nogueron (GGN), Yves Henrotin, Rositsa Karalilova (RK), Sylvia Nuernberger(SN), Cecilia Aulin(CA), Josefine E Naili(JN), Peter Balint(PB); Writing—review and editing: all authors.All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicant.

Consent for publication

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Competing interests

The authors declare no competing interests.

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References

1. Hunter DJ, Bierma-Zeinstra S, Osteoarthritis. The Lancet. 2019;393(10182).
2. Schulze TG, McMahon FJ. Defining the phenotype in human genetic studies: Forward genetics and reverse phenotyping. In: Human Heredity. 2004.
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;26(3).
4. Castaneda S, Roman-Blas JA, Largo R, Herrero-Beaumont G. Osteoarthritis: a progressive disease with changing phenotypes. Rheumatology. 2014;53(1).
5. Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H et al. Osteoarthr Lancet. 2015;386(9991).
6. Mobasheri A, Rayman MP, Gualillo O, Sellam J, van der Kraan P, Fearon U. The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2017;13(5).
7. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11).
8. Iijima H, Fukutani N, Aoyama T, Fukumoto T, Uritani D, Kaneda E et al. Clinical phenotype classifications based on static varus alignment and varus thrust in Japanese patients with medial knee osteoarthritis. Arthritis Rheumatol. 2015;67(9).
9. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7).
10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5. https://doi.org/10.1007/s10654-010-9491-z.
11. Knoop J, van der Leeden M, Thorstensson CA, Roorda LD, Lems WF, Knol DL et al. Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2011;63(11).
12. Castañeda S, Roman-Blas JA, Largo R, Herrero-Beaumont G. Subchondral bone as a key target for osteoarthritis treatment. Biochemical Pharmacology. 2012 Elsevier Inc. 83:315–23.
13. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthritis Rheum. 2013;65(2).
14. Hawker GA, Stanaitis I. Osteoarthritis year in review 2014: clinical. Osteoarthritis Cartilage. 2014;22(12).
15. Thomas MJ, Peat G, Rathod T, Marshall M, Moore A, Menz HB et al. The epidemiology of symptomatic midfoot osteoarthritis in community-dwelling older adults: Cross-sectional findings from the clinical assessment study of the foot. Arthritis Res Ther. 2015;17(1).
16. Van der Esch M, Knoop J, van der Leeden M, Roorda LD, Lems WF, Knol DL, et al. Clinical phenotypes in patients with knee osteoarthritis: A study in the Amsterdam osteoarthritis cohort. Osteoarthritis Cartilage. 2015;23(4):544–9.
17. Waarsing JH, Bierma-Zeinstra SMA, Weinans H. Distinct subtypes of knee osteoarthritis: data from the osteoarthritis initiative. Rheumatol (United Kingdom). 2015;54(9):1650–8.
18. Wesseling J, Bastick AN, ten Wolde S, Kloppenburg M, Lafeber FPJG, Bierma-Zeinstra SMA et al. Identifying trajectories of pain severity in early symptomatic knee osteoarthritis: A 5-year followup of the cohort hip and cohort knee (CHECK) study. J Rheumatol. 2015;42(8).
19. Raynauld J, Pelletier J, Roubille C, Dorais M, Abram F, Li W et al. Magnetic resonance Imaging–Assessed Vastus medialis muscle fat content and risk for knee osteoarthritis progression: relevance from a clinical trial. Arthritis Care Res (Hoboken). 2015;67(10).
20. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyère O et al. Diabetes is a risk factor for knee osteoarthritis progression. Osteoarthritis Cartilage. 2015;23(6).
21. Dell'Isola A, Allan R, Smith SL, Marreiros SSP, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016;17(1).
22. Kittelson AJ, Stevens-Lapsley JE, Schmiege SJ. Determination of pain phenotypes in knee osteoarthritis: A latent class analysis using data from the osteoarthritis initiative. Arthritis Care Res (Hoboken). 2016;68(5).
23. Cardoso JS, Riley JL, Glover T, Sibille KT, Bartley EJ, Goodin BR et al. Experimental pain phenotyping in community-dwelling individuals with knee osteoarthritis. Pain. 2016;157(9).
24. Frey-Law LA, Bohr NL, Sluka KA, Herr K, Clark CR, Noiseux NO et al. Pain sensitivity profiles in patients with advanced knee osteoarthritis. Pain. 2016;157(9).
25. Messier SP, Beavers DP, Herman C, Hunter DJ, DeVita P. Are unilateral and bilateral knee osteoarthritis patients unique subsets of knee osteoarthritis? A Biomechanical perspective. Osteoarthritis Cartilage. 2016;24(5).
26. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis Cartilage. 2017;25(12).
27. Herrero-Beaumont G, Roman-Blas JA, Bruyère O, Cooper C, Kanis J, Maggi S et al. Clinical settings in knee osteoarthritis: pathophysiology guides treatment. Maturitas. 2017;96.
28. Dell'Isola A, Steultjens M. Classification of patients with knee osteoarthritis in clinical phenotypes: data from the osteoarthritis initiative. PLoS ONE. 2018;13(1).
29. Bay-Jensen AC, Thudium CS, Gualillo O, Mobasheri A. Biochemical marker discovery, testing and evaluation for facilitating OA drug discovery and development. Drug Discov Today. 2018;23(2).
30. Büchele G, Günther KP, Brenner H, Puhl W, Stürmer T, Rothenbacher D et al. Osteoarthritis-patterns, cardio-metabolic risk factors and risk of all-cause mortality: 20 years follow-up in patients after hip or knee replacement. Sci Rep. 2018;8(1).
31. Mobasheri A, Saarakkala S, Finnilä M, Karsdal MA, Bay-Jensen AC, van Spil WE. Recent advances in Understanding the phenotypes of osteoarthritis. F1000Res. 2019;8.
32. Teixeira PEP, Zehry HI, Chaudhari S, Dipietro L, Fregni F. Pain perception in chronic knee osteoarthritis with varying levels of pain inhibitory control: an exploratory study. Scand J Pain. 2020;20(4).
33. Miles C, Greene A. The effect of treatment with a non-invasive foot worn Biomechanical device on subjective and objective measures in patients with knee osteoarthritis- a retrospective analysis on a UK population. BMC Musculoskelet Disord. 2020;21(1).
34. Bennell KL, Nelligan RK, Kimp AJ, Schwartz S, Kasza J, Wrigley TV et al. What type of exercise is most effective for people with knee osteoarthritis and co-morbid obesity? The TARGET randomized controlled trial. Osteoarthritis Cartilage. 2020;28(6).
35. Munugoda IP, Pan F, Wills K, Mattap SM, Cicuttini F, Graves SE et al. Identifying subgroups of community-dwelling older adults and their prospective associations with long-term knee osteoarthritis outcomes. Clin Rheumatol. 2020;39(5).

36. Kittelson AJ, Schmiege SJ, Maluf K, George SZ, Stevens-Lapsley JE. Determination of pain phenotypes in knee osteoarthritis using latent profile analysis. Pain Med (United States). 2021;22(3):653–62.
37. Xu T, Jia X, Chen S, Xie Y, Tong KK, Iezzi T et al. Physical activity and sleep differences between osteoarthritis, rheumatoid arthritis and non-arthritic people in China: objective versus self report comparisons. BMC Public Health. 2021;21(1).
38. Knoop J, Ostelo RWJG, van der Esch M, de Zwart A, Bennell KL, van der Leeden M et al. Construct validity of the OCTOPuS stratification algorithm for allocating patients with knee osteoarthritis into subgroups. BMC Musculoskelet Disord. 2021;22(1).
39. Berna, Güzel. Mehmet Derya Demirağ, Düriye Sıla Karagöz Özen, Nizamettin Güzel, mukadder Erdem, Berna Göker. Associations between the radiographic phenotypes and the presence of metabolic syndrome in patients with knee osteoarthritis. Turk J Med Sci. 2021;51(5):2461–6.
40. Guehring H, Moreau F, Daelken B, Ladel C, Guenther O, Bihlet AR et al. The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the FORWARD knee osteoarthritis trial. Semin Arthritis Rheum. 2021;51(2).
41. Fawole H, Felson D, Frey-Law L, Jafarzadeh S, Dell'Isola A, Steultjens M et al. Is the association between physical activity and fatigue mediated by physical function or depressive symptoms in symptomatic knee osteoarthritis? The multicenter osteoarthritis study. Scand J Rheumatol. 2021;50(5).
42. Zhu Z, Hu G, Jin F, Yao X. Correlation of osteoarthritis or rheumatoid arthritis with bone mineral density in adults aged 20–59 years. J Orthop Surg Res. 2021;16(1).
43. Nishigami T, Tanaka S, Mibu A, Imai R, Wand BM. Knee-related disability was largely influenced by cognitive factors and disturbed body perception in knee osteoarthritis. Sci Rep. 2021;11(1).
44. Duarte-Salazar C, Marín-Arriaga N, Miranda-Duarte A. The high clinical burden of erosive hand osteoarthritis is associated with clinical findings, pain, and radiographic severity. Reumatología Clínica (English Edition). 2022;18(6).
45. Hess S, Moser LB, Robertson EL, Behrend H, Amsler F, Iordache E et al. Osteoarthritic and non-osteoarthritic patients show comparable coronal knee joint line orientations in a cross-sectional study based on 3D reconstructed CT images. Knee Surgery, Sports Traumatology, Arthroscopy. 2022;30(2).
46. Knoop J, de Joode JW, Brandt H, Dekker J, Ostelo RWJG. Patients' and clinicians' experiences with stratified exercise therapy in knee osteoarthritis: a qualitative study. BMC Musculoskelet Disord. 2022;23(1).
47. Nelson AE, Keefe TH, Schwartz TA, Callahan LF, Loeser RF, Golightly YM et al. Biclustering reveals potential knee OA phenotypes in exploratory analyses: data from the osteoarthritis initiative. PLoS ONE. 2022;17(5).
48. Hangaard S, Boesen M, Bliddal H, Wirth W. Do Ahlbäck scores identify subgroups with different magnitudes of cartilage thickness loss in patients with moderate to severe radiographic osteoarthritis? One-year follow-up data from the osteoarthritis initiative. Skeletal Radiol. 2022;51(4).
49. Pihl K, Roos EM, Taylor RS, Grønne DT, Skou ST. Prognostic factors for health outcomes after exercise therapy and education in individuals with knee and hip osteoarthritis with or without comorbidities: A study of 37,576 patients treated in primary care. Arthritis Care Res (Hoboken). 2022;74(11).
50. Stamenkovic BN, Rancic NK, Bojanovic MR, Stojanovic SK, Zivkovic VG, Djordjevic DB et al. Is osteoarthritis always associated with low bone mineral density in elderly patients?? Med (B Aires). 2022;58(9).
51. Cao T-N, Huynh K-N, Tran H-T. Nguyen. Association between asymptomatic hyperuricemia and knee osteoarthritis in older outpatients. Eur Rev Med Pharmacol Sci. 2022;26(18):6600–7.
52. Binvignat M, Pires G, Tchitchek N, Costantino F, Courties A, Klatzmann D et al. Identification of symptom phenotypes of hand osteoarthritis using hierarchical clustering: results from the DIGICOD cohort. Arthritis Care Res (Hoboken). 2023;75(7).
53. Copp G, Robb KP, Viswanathan S. Culture-expanded mesenchymal stromal cell therapy: does it work in knee osteoarthritis? A pathway to clinical success. Cell Mol Immunol. 2023;20(6).
54. Jansen NEJ, Molendijk E, Schiphof D, van Meurs JBJ, Oei EHG, van Middelkoop M, et al. Metabolic syndrome and the progression of knee osteoarthritis on MRI. Osteoarthritis Cartilage. 2023;31(5):647–55.
55. Demanse D, Saxer F, Lustenberger P, Tankó LB, Nikolaus P, Rasin I et al. Unsupervised machine-learning algorithms for the identification of clinical phenotypes in the osteoarthritis initiative database. Semin Arthritis Rheum. 2023;58.
56. Feng Jling, Ma R, han, Sun L, li, Zhao Jru, Zhao Y ping, Li G. Quantitative assessment of condylar bone resorption using fused CBCT images: differentiating and diagnosing three distinct groups based on volume and thickness decrease. Dentomaxillofacial Radiology. 2023;52(8).
57. Gonzalez FF, Leporace G, Franciozi C, Cockrane M, Metsavaht L, Carpes FP et al. Clinical and radiographic characterization of three-dimensional gait profiles of patients with knee osteoarthritis. Knee. 2023;44.
58. Sharma K, Eckstein F, Maschek S, Roth M, Hunter DJ, Wirth W. Association of quantitative measures of medial meniscal extrusion with structural and symptomatic knee osteoarthritis progression– Data from the OAI FNIH biomarker study. Osteoarthritis Cartilage. 2023;31(10).
59. Hart HF, Birmingham TB, Sritharan P, Primeau C, King MG, Fischer LK. Sex-related differences in gait characteristics and their associations with symptoms in individuals with patellofemoral osteoarthritis. Gait Posture. 2024;107.
60. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. Osteoarthritis and Cartilage. 2017 W.B. Saunders Ltd; 25:1926–41.

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